VOLUME 61 • MAY 1959 • NUMBER 5

OPHTHALMOLOGY

The Symposium on the Transparency of the Cornea
David G. Cogan

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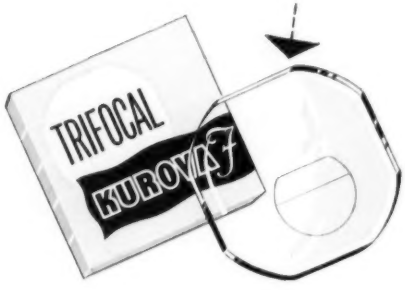

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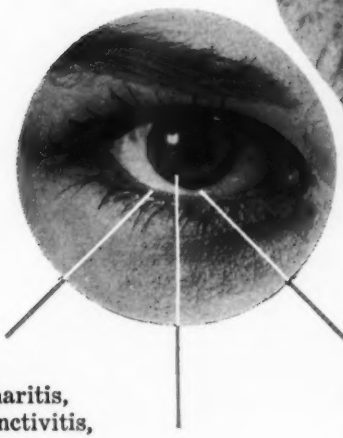

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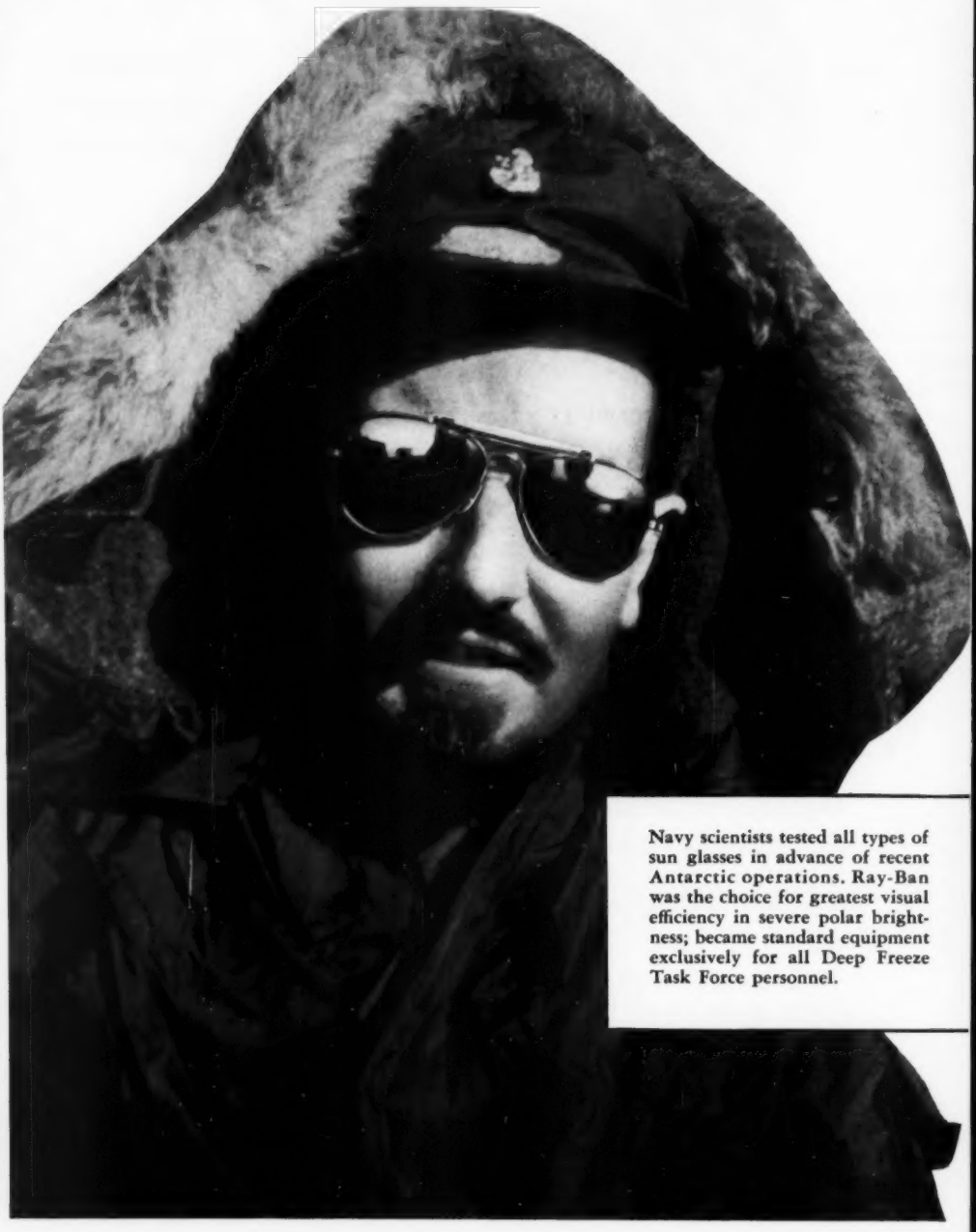

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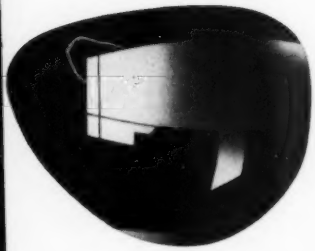

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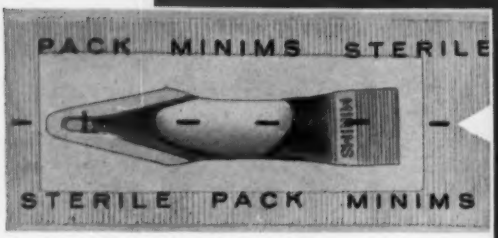

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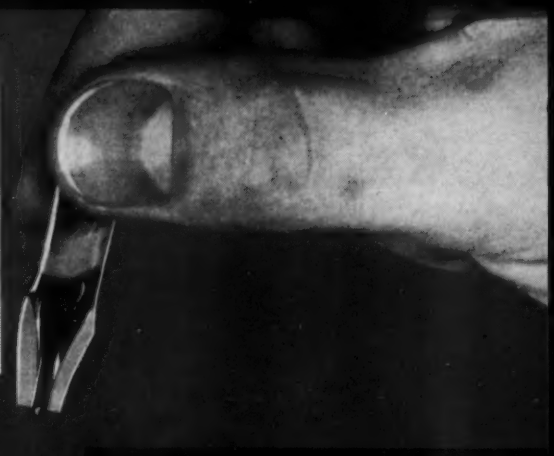

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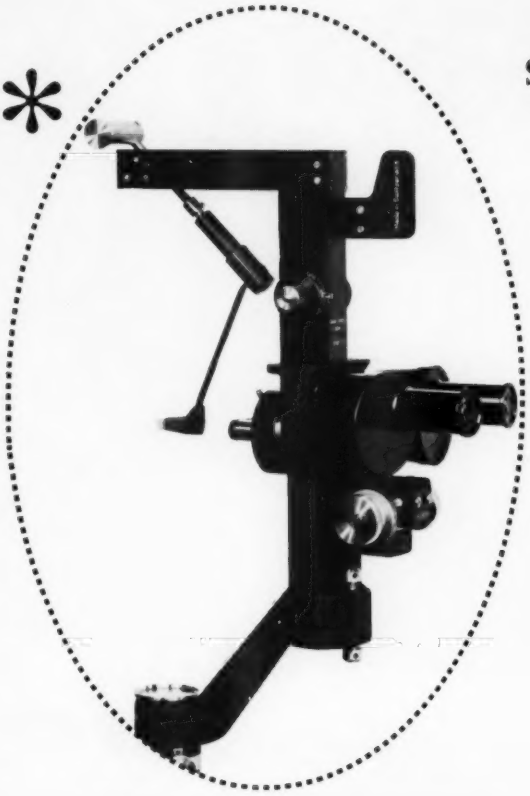

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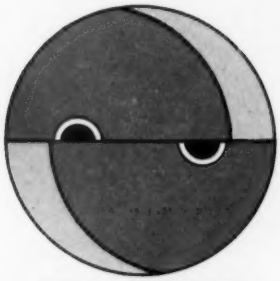

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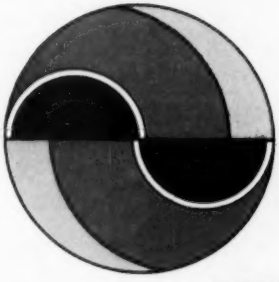

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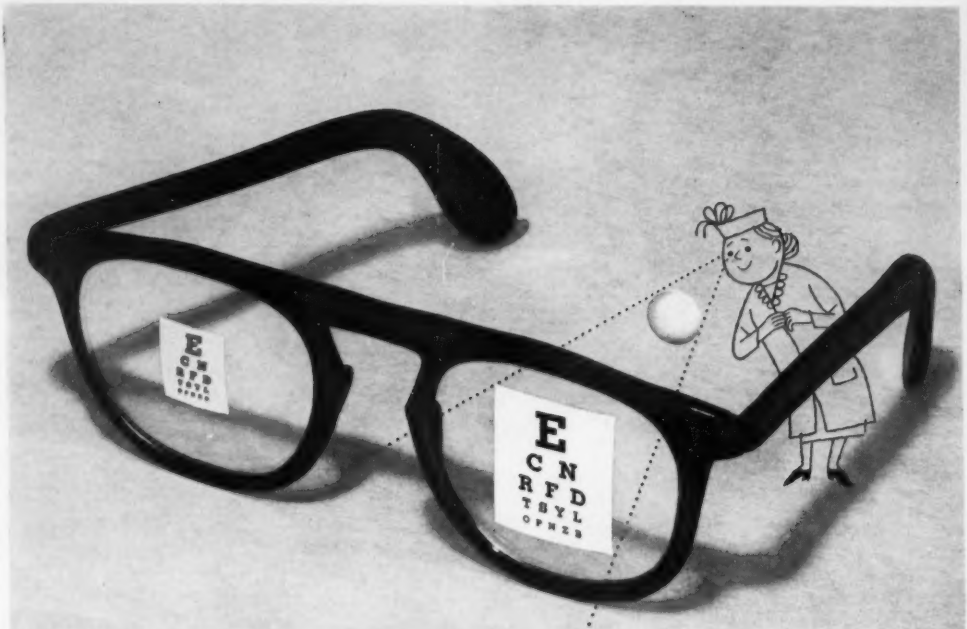

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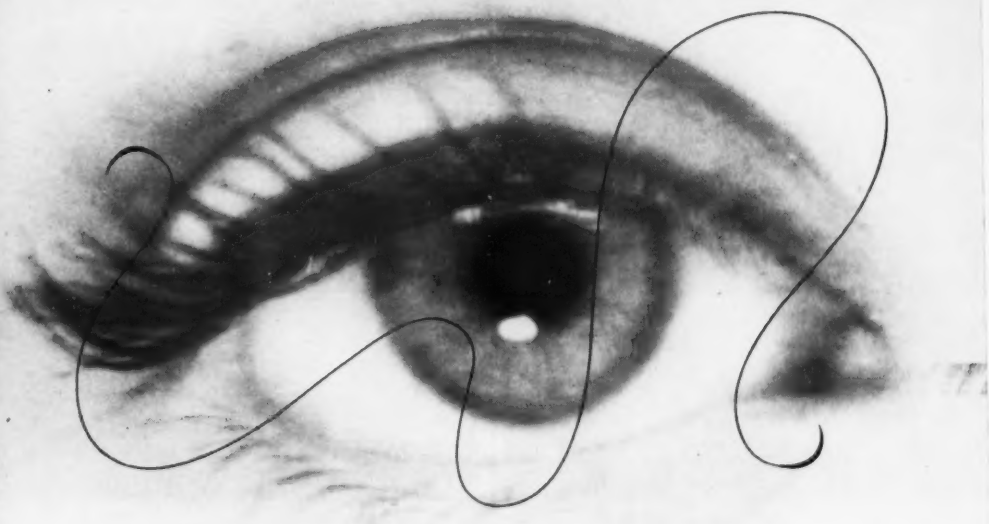

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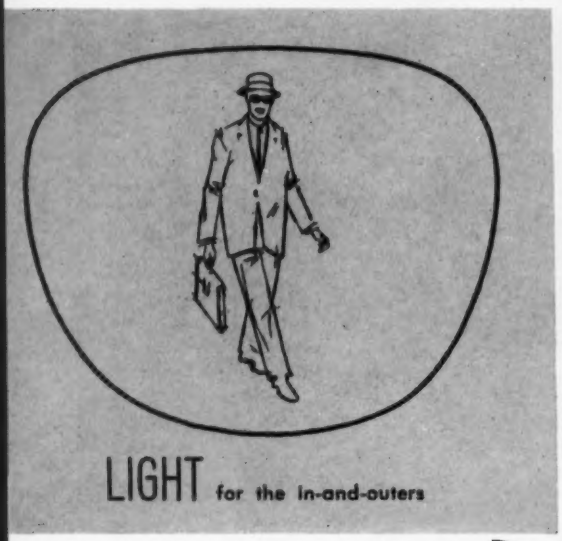

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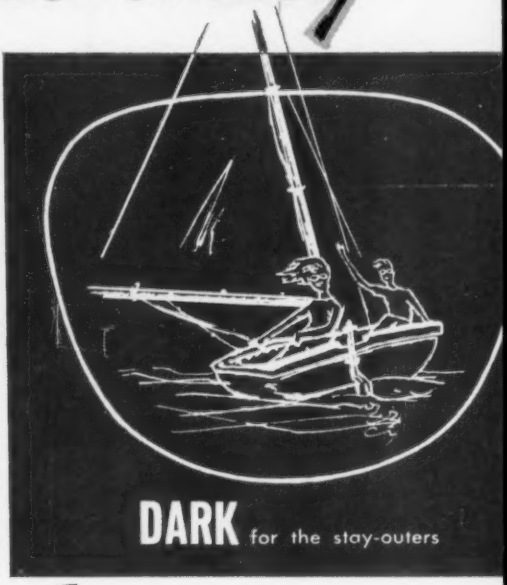

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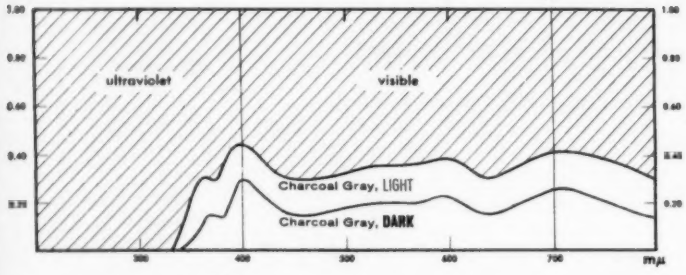

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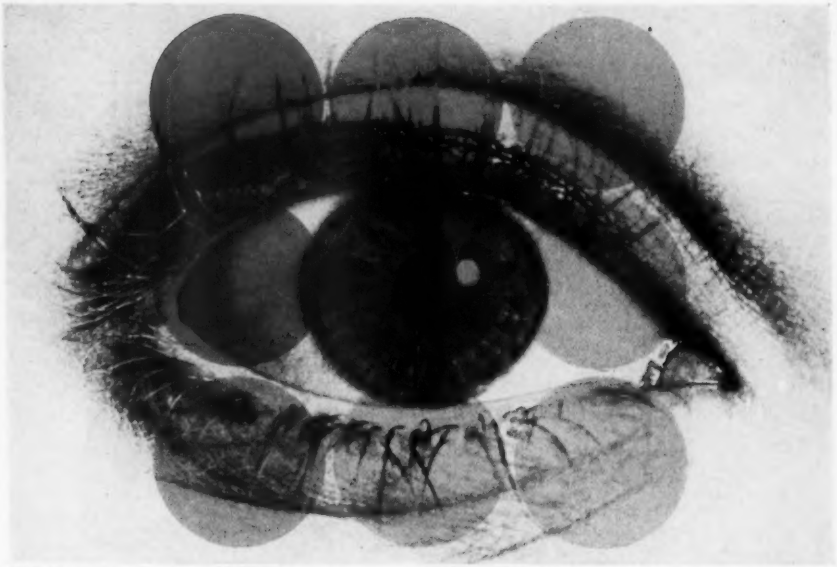

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1. New and Nonofficial Drugs; J. B. Lippincott Company, Philadelphia, 1958, p. 243.

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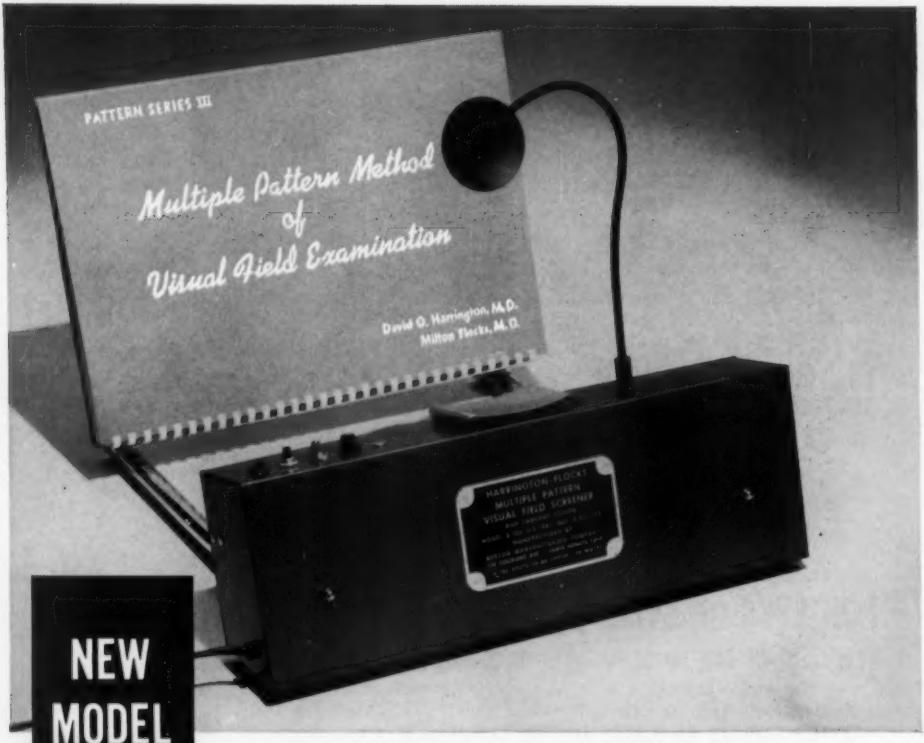

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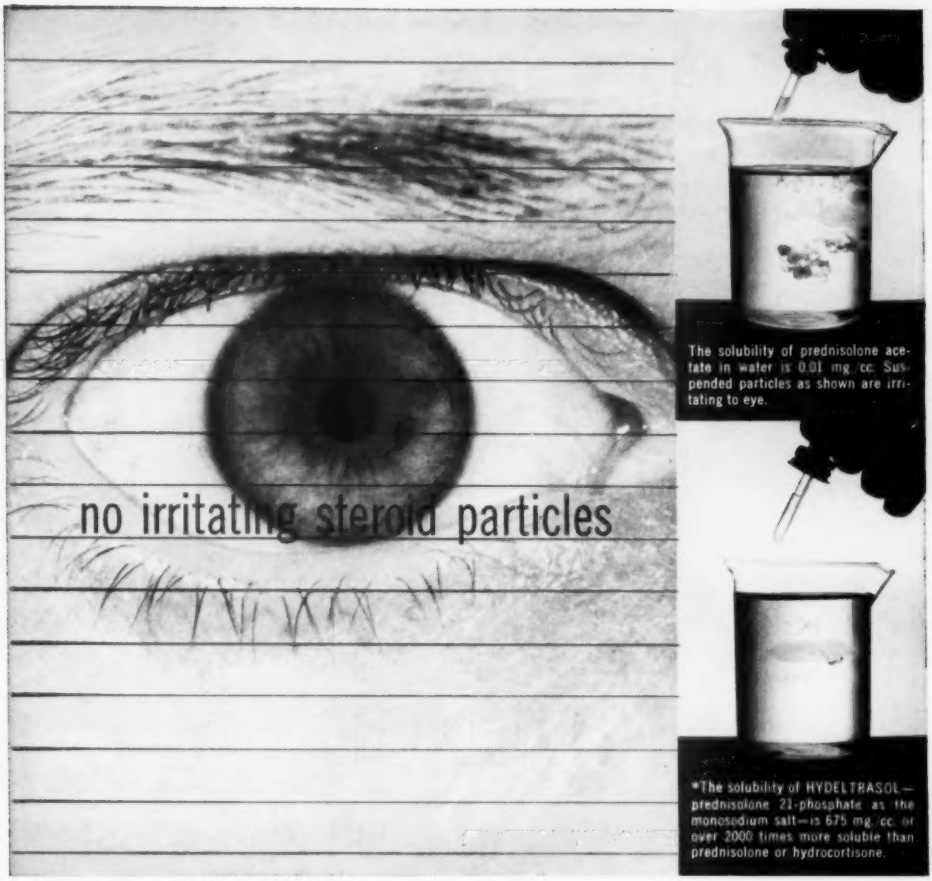
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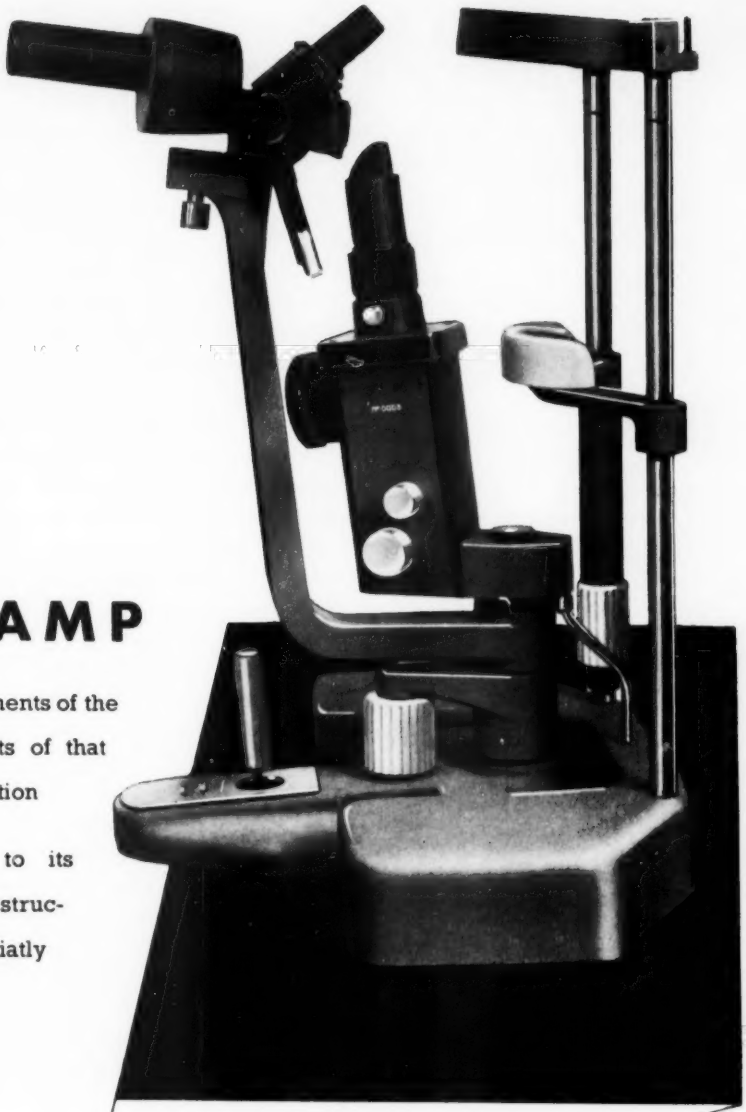

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HIGHLIGHTS FROM THE A.M.A. COUNCIL ON DRUGS

REPORT ON TRIAMCINOLONE

J.A.M.A. 169:257 (January 17) 1959.

"It [triamcinolone] has an anti-inflammatory potency greater than an equal amount of prednisolone; i.e., comparable suppressive effects may usually be achieved with lower doses of triamcinolone than with prednisolone."

"Triamcinolone lacks the sodium-retaining and edema-producing effects of most other glucocorticoids. During the first several days of administration, it may cause a loss of sodium from the body; an initial mild diuretic action is frequently observed, whether the patient is frankly edematous or not. This is in contrast to the definite sodium-retaining and fluid-retaining properties of cortisone and hydrocortisone and to a much lesser extent with prednisone and prednisolone."

"Except in exceedingly large doses, triamcinolone apparently has no consistent effect on potassium excretion. Hence, neither sodium restriction nor potassium supplementation is ordinarily required during therapy with this agent."

"As with other glucocorticoids, the long-term administration of triamcinolone results in definite catabolic effects, as indicated by impairment of carbohydrate utilization and negative protein and calcium balance. This catabolic effect, coupled with a lack of appetite stimulation which is apparently peculiar to triamcinolone, may produce weight loss that might be undesirable in some patients treated for long periods of time."

"...the voracious appetite, with weight gain and euphoria, characteristic of other steroids, is not seen with administration of triamcinolone."

"Triamcinolone has been used for the management of a wide variety of clinical conditions usually considered amenable to systemic steroid therapy. These have included rheumatoid arthritis and other collagen diseases, allergic and dermatological disorders, certain leukemias and malignant lymphomas, the nephrotic syndrome, pulmonary emphysema and fibrosis, acute bursitis, rheumatic fever, and certain blood dyscrasias. Although clinical experience with the drug in some of the foregoing conditions is not extensive, the many similarities in action between triamcinolone and other potent glucocorticoids would indicate a usefulness for triamcinolone akin to that of other agents of this class."

"There is some evidence that triamcinolone is more effective at a smaller dosage than are other steroids in controlling both the skin and joint lesions in psoriasis, whether or not complicated by arthropathy."

"Triamcinolone appears to compare favorably with other steroids for use in those situations in which edema and sodium retention have been complicating problems."

"It [triamcinolone] may also be the steroid of choice for patients in whom psychic stimulation, euphoria, voracious appetite, and weight gain should be avoided."

"...the drug [triamcinolone] does produce the other side effects and untoward reactions common to the glucocorticoids. At therapeutically equivalent doses, the frequency and severity of clinical manifestations of hyperadrenalism — rounding of the face, fat deposition, and hirsutism — are essentially the same. Likewise, there is little indication that the relative incidence of osteoporosis is materially decreased after the long-term use of the drug."

"Triamcinolone apparently does not cause the euphoria sometimes seen with other steroids, and the occurrence of mental depressions is uncommon."

"Current evidence suggests that the drug [triamcinolone] may not produce as high an incidence of peptic ulcer as do other steroids."

"Cutaneous erythema seems to be a side effect peculiar to triamcinolone."

"The usual contraindications and precautions of glucocorticoid therapy should be followed in the use of triamcinolone, keeping in mind that prolonged therapy with this drug will suppress the function of the patient's own adrenals by interfering with the pituitary-adrenal axis."

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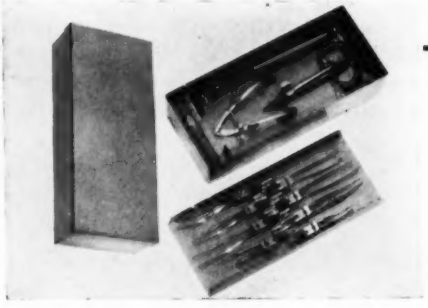

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Caution: Prednisolone should not be used in herpes simplex.

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1. GIFFORD S. R.: OCULAR THERAPEUTICS, 4TH ED., LEA & FEBIGER, PP. 253-256 • 2. HAMBURGER,, C.: ZU DER NEUEN GLAUKOMBEHANDLUNG. KLIN. MONATSBL. F. AUGENH., 72:47, 1924 • 3. DUKE-ELDER, W. S. AND LAW, F. W.: TREATMENT OF GLAUCOMA BY ADRENALINE AND HISTAMINE. BRIT. MED. JNL., 1:590, 1929

Editorials

The Symposium on the Transparency of the Cornea

That type of meeting called symposium, in which a selected few gather to discuss some topic of mutual interest, seems to be the mode of our times. The occasion of the recent International Congress of Ophthalmology in Brussels stimulated the holding of several such symposia having no official connection with the Congress itself and being held in various parts of Europe either before or after the Congress.

One of these symposia, "The Transparency of the Cornea," was organized by Sir Stewart Duke-Elder under the auspices of the Council for International Organizations of Medical Sciences. It was the second symposium to be held under such auspices and, like the first ("Glaucoma," 1954), the presentations are to be published in book form. This symposium was held over a five-day period in one of Belgium's deluxe hotels at the coastal resort of Kokke-Le Zoute. The chairman maintained an atmosphere of informality and good-natured give-and-take.

The opening presentation was appropriately that of Belgium's François and Rabaey (Ghent) on the microscopic and ultramicroscopic features of the cornea. This was followed by Smelser (New York), reporting his extensive studies on the deposition in the cornea of radioactive sulfate as an index of polysaccharide formation. Maurice (London) presented his lattice theory of corneal transparency in which light is thought to be scattered in the cornea in such a way as would occur in a diffraction grating so that light would be transmitted in the forward direction only. Then van Walbeek (Amsterdam) discussed turgescence and swelling, likening the cornea to reinforced concrete in which the collagen provided the more rigid supports and the mucoid provided the surrounding ground substance. Incidentally, van Walbeek could not resist pointing out that it was Loewenhoek, a compatriot and the father of microscopy, who first pointed out the swelling capacity of the cornea. This was in 1687!

The second day was occupied in part by a cross exchange of discussions led by Harris (Portland, Ore.) and Langham (London) on those metabolic processes in the cornea thought to be responsible for the maintenance of the normally deturgesced state. Weimar (New York) presented her studies showing that invasion of the cornea by monocytes and activation of the stromal cells in wound healing resulted from a factor in epithelial breakdown. Ashton (London) discussed the mechanism of neovasculogenesis in the cornea, postulating both a mechanical factor and a vasoformative factor, and compared the process to that occurring in the retina.

The third day was devoted in part to a presentation of certain fat studies on the cornea by Cogan (Boston) and in part to an informal relaxation in which the group was hospitably entertained at the home of Dr. Jules François.

The fourth and final day of formal presentations centered about corneal grafts with Dohlman (Lund, Sweden), discussing the methods of preservation of the cornea and the fate of the various components of the grafted implant.

Maumanee (Baltimore) presented the case for immune reactions as being one of the main causes for delayed opacification of the graft. Leigh (London) described clinical reactions in donor and recipient corneas, and Paufique (Lyons, France) compared the clinical aspects of lamellar and penetrating keratoplasty. Finally, Franceschetti (Geneva) described the fate of scleral implants in the cornea.

The final day of this symposium was set aside for free discussions. All agreed that the sessions had provided an international forum for airing both old and new ideas about the cornea and in so doing had served a most useful function.

DAVID G. COGAN, M.D.

A.M.A. ARCHIVES OF
OPHTHALMOLOGY

Unilateral Lid Retraction Without Exophthalmos

A Manifestation of Thyroid System Dysfunction

JOHN M. McLEAN, M.D., and EDWARD W. D. NORTON, M.D., New York

The clinical picture of unilateral retraction of the upper lid of one eye without other ocular abnormalities is so characteristic that it is immediately recognized by the examiner once he is aware of the entity. In this type of lid retraction, the margin of one of the upper eyelids is elevated above the limbus so that a band of sclera is readily visible on forward gaze (Fig. 1*A*). This elevation of the lid decreases on upward gaze and becomes more apparent on downward gaze (Fig. 1*B*). In addition to the retraction of the lid margin, there is marked prominence of the lid fold on downward gaze (Fig. 1*B*). The position of the lower lid margin is usually unaffected but may be slightly elevated (Fig. 2). These changes in the lids have been described in detail by Pochin.[1-3]

The aims of the present study were to determine the course and pathogenesis of unilateral lid retraction and its relationship to any systemic illness. Observations were made on 12 patients seen over a period of eight years at the New York Hospital-Cornell Medical Center. These patients were selected because they presented the following features: (1) unilateral lid retraction, (2) no significant exophthalmos[4] as measured by the Krahn modification of the Hertel exophthalmometer, and (3) normal ocular motility.

Submitted for publication June 26, 1958.

Presented at the 94th Annual Meeting of the American Ophthalmological Society, May 28, 1958.

From the Department of Surgery (Ophthalmology), The New York Hospital-Cornell Medical Center.

Observations

After extensive medical, neurological, and roentgenological studies, the only evidences of abnormalities encountered were

Fig. 1.—Right unilateral lid retraction showing baring of sclera and accentuated lid fold. *A*, forward gaze; *B*, downward gaze.

Fig. 2.—Left unilateral lid retraction showing apparent elevation of the lower lid margin.

those of thyroid dysfunction. At the time of the first examination five of the patients were definitely toxic. Four patients were euthyroid at the time of the initial work-up but became clearly toxic during the first year of follow-up. Three patients, one of whom has been followed seven years, have not yet shown evidence of toxicity. It is of interest that at the time of the initial examination three of the four patients who became toxic under observation had a positive triiodothyronine suppression test as described by Werner.[5] Two of the patients who have not shown evidence of toxicity had a negative or borderline suppression test.

Since no other explanation for the unilateral lid retraction has presented itself during the period of follow-up, we are convinced, as was Pochin,[3] that this sign is definite evidence of some form of thyroid system dysfunction. The nature of the dysfunction is not yet understood, but it does not appear to be closely related to toxicity or exophthalmos.

Nine of the patients have been followed two or more years. Only one has had complete regression of the lid retraction; four

Fig. 3.—Reduction of lid retraction over a seven-year period. No treatment. *A*, left unilateral lid retraction, 1951, forward gaze; *B*, left unilateral lid retraction, 1951, downward gaze; *C*, left unilateral lid retraction, 1958, forward gaze; *D*, left unilateral lid retraction, 1958, downward gaze.

Fig. 4.—Left unilateral lid retraction 15 minutes after instillation of two drops of phenylephrine 10% in a normal subject. *A*, forward gaze; *B*, downward gaze.

have shown marked improvement (Fig. 3), while three remain unchanged. The rate and degree of improvement were not closely related to the clinical response to antithyroid therapy.

Five of the twelve patients were referred with the clinical diagnosis of orbital tumor. We believe that the widening of the palpebral fissure as a result of the lid retraction misled the examiners into thinking they were dealing with a case of unilateral exophthalmos. The absence of obvious signs of thyroid toxicity compounded this confusion. Once one is familiar with this condition, no confusion will arise in the differential diagnosis. The one entity that might imitate it is the pseudo-Graefe sign seen in aberrant regeneration; however, the history and evidence of previous third nerve paresis should make this diagnosis apparent.

These cases of unilateral lid retraction offer a unique opportunity to compare the normal with the abnormal in the same person. Therefore, we have studied these patients in an attempt to evaluate the four basic mechanisms that have been suggested[2,6,7] to explain lid retraction in patients with thyroid dysfunction.

1. *Overactivity of Sympathetic Nervous System.*—This has been suggested ever since Bernard published his observations on animals.[8] The only evidence we could produce in the human to support this idea was the fact that when sympathomimetic drugs, such as phenylephrine (10%), were instilled into the conjunctival sac of one eye in normal persons, a clinical picture of unilateral lid retraction was produced (Fig. 4). However, this did result in dilatation of the homolateral pupil, something that is never seen in the spontaneously occurring case. Stellate ganglion blocks performed on three of the patients in this study produced a definite Horner's syndrome, showing the effectiveness of the block. The lid retraction was not relieved; there was only an apparent improvement because of the ptosis (Fig. 5). Recently it has been suggested that reserpine relieves lid retraction associated with thyroid dysfunction.[9] Presumably this effect results from the action of the drug on the sympathetic nervous system. One patient in this study was admitted to the hospital and given 2.5 mg. of reserpine intramuscularly every six hours for 48 hours. A bilateral ptosis with miosis resulted; however, the unilateral lid retraction persisted (Fig. 6).

2. *Overactivity of Levator Associated with Paresis of Upward Gaze.*—This factor is obviously not pertinent in a study of this type of lid retraction. All of our patients had normal eye movements. This mechanism is important in those cases of thyroid dysfunction associated with ophthalmoplegia and in those cases of lid retraction associated with midbrain disease.

3. *Spasm of Levator Muscle of Eyelid.*—This has been proposed by Pochin[3] and by Rundle.[6] It is difficult to conceive of a muscle being in spasm year in and year out with essentially no evidence of variability,

Fig. 5.—Effect of stellate ganglion block on left unilateral lid retraction. *A*, before sympathetic block, forward gaze; *B*, before sympathetic block, downward gaze; *C*, after sympathetic block, forward gaze; *D*, after sympathetic block, downward gaze. Note persistence of the lid fold on the left.

Fig. 6.—Effect of reserpine on unilateral lid retraction. *A*, before reserpine treatment, forward gaze; *B*, before reserpine treatment, downward gaze; *C*, after reserpine treatment, forward gaze; *D*, after reserpine treatment, downward gaze. Note the persistence of retraction on the right despite the development of bilateral ptosis.

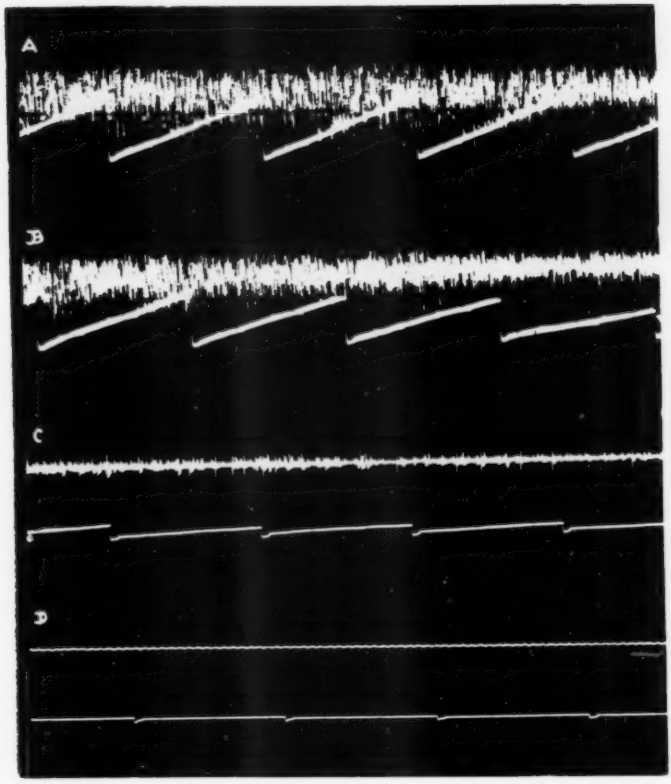

Fig. 7. — Electromyogram on patient with right unilateral lid retraction. Upper trace: EMG right levator; lower trace: integrator. A-D: gaze up to gaze down. No activity gaze down despite persistence of lid retraction. There was no difference between the EMG on the right when compared with the left.

so we were reluctant to accept this explanation. François [10] has suggested that excitation of midbrain structures by thyrotropic hormone results in overactivity of the striated levator muscle. Electromyographic studies were carried out on four of these patients by Dr. Goodwin Breinin (Fig. 7). The levator muscle of the retracted lid showed no evidence of increased activity when compared with the levator on the uninvolved side. The normal inhibition of neuromuscular activity that occurs in the levator muscle on looking down was identical on the two sides (Fig. 7).

4. *Mechanical Changes in Levator Muscle.*—These have been suggested by Meadows [7] as a basis for this phenomenon. Observations on unilateral lid retraction during sleep and anesthesia have shown a persistence of the retraction.[1] Retrobulbar blocks were carried out on two patients in an effort to completely interrupt the innervation of the elevating muscles of the upper lid. The lid retraction was not relieved (Fig. 8).

Comment

These observations establish that the mechanism of unilateral lid retraction associated with thyroid dysfunction is not innervational in origin. The most logical explanation is that the lid retraction is secondary to changes in the levator muscle itself. We have no good evidence as to what these changes are other than knowing that they are reversible.

Fig. 8.—Persistence of right lid retraction despite complete paralysis of the levator muscle after a retrobulbar block. *A*, before block, forward gaze; *B*, before block, downward gaze; *C*, after block, upward gaze; *D*, after block, downward gaze. Note the failure to obtain complete closure of the fissure.

Summary

Unilateral lid retraction without other ocular abnormalities is a manifestation of some type of thyroid system dysfunction not yet understood. It is not related to clinical evidence of toxicity or exophthalmos.

Unilateral lid retraction tends to improve slowly over the course of years.

Unilateral lid retraction is not innervational in origin; it is probably secondary to changes in the levator muscle.

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Internuclear Ophthalmoplegia

A Review of Fifty-Eight Cases

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The syndrome of internuclear ophthalmoplegia is a characteristic disturbance of ocular motility which has considerable value in topical and etiologic diagnosis. It has been described a number of times, but we are not aware of a comprehensive study of the associated clinical findings or of a determination of the prognosis. Classification of the entity has also been somewhat obscured by varying terminology in the literature. The purpose of this report is to discuss briefly the nomenclature of this syndrome and to present the ophthalmologic and neurologic findings in a series of 58 cases of internuclear ophthalmoplegia.

Nomenclature

Lhermitte,[1] in 1922, is cited[2] as the first to use the term "ophthalmoplegia internuclearis." However, Leslie Paton,[3] in 1921, had stated, "the dorsal longitudinal bundle is of such great clinical importance that I have ventured in the classification of ocular palsies to put in a separate class of 'internuclear palsies.' One of its functions is to bring the action of the external rectus of one eye into relationship with the internal rectus of the opposite eye. As is well known, a lesion in the abducens nucleus or its neighborhood produces not only loss of outward movement of the eye on the affected side, but a defect in the action of the internal rectus of the other eye, only observable in conjugate lateral movement to the affected side and not present in convergence." Although thus describing a paresis of conjugate gaze, Paton gave no specific references and cited no cases, but he did attempt to delineate clinically those cases with lesions of the medial longitudinal fasciculus. In 1923, Lutz[4] divided internuclear ophthalmoplegia into two clinical types: the anterior and posterior internuclear palsies. Duke-Elder[2] cites Lutz in the following definitions: "In *anterior* internuclear palsies the externus on the side of the lesion functions normally (or restrictedly), but the contralateral internus is paralysed for conjugate movements towards the side of the lesion and at the same time functions normally in convergence. In *posterior* internuclear palsies, on the other hand, both internal recti function normally in convergence and in lateral conjugate movements, but the externus on the side of the lesion is paralysed for conjugate movements."

The so-called posterior internuclear ophthalmoplegia of the Lutz classification thus may mimic a simple sixth-nerve palsy, and abduction of the eye must occur with labyrinthine stimulation if one is to differentiate the former. As no unequivocal case of this posterior type had been reported,[5] one of us (D. G. C.) has proposed a different classification of these cases based on the presence or absence of convergence and of associated conjugate gaze palsy. Thus, in *anterior* internuclear ophthalmoplegia there is impairment of convergence associated with paralysis of the medial rectus on horizontal conjugate gaze toward the side opposite the lesion. *Posterior* internuclear ophthalmoplegia is that condition in which convergence is unaffected despite paralysis of the medial rectus in conjugate horizontal

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gaze. It should be stressed that in this classification there is weakness of the *ipsilateral medial* rectus muscle on horizontal gaze in both types of internuclear palsy, and there is characteristically a predominantly monocular nystagmus seen in the abducting eye. The latter feature has led some authors[6] to employ the term "ataxic nystagmus" for this syndrome.

There is general agreement that the medial longitudinal fasciculus is the site of the lesion producing a paralysis of the medial rectus in conjugate gaze and yet sparing it in convergence. There has been disagreement, however, in the unilateral cases as to whether the lesion is ipsilateral or contralateral to the affected medial rectus. Relatively few cases of internuclear ophthalmoplegia have been studied anatomically, and most of these do not provide information on the laterality because both sides were involved. Spiller,[7] in 1924, reported the first case of internuclear ophthalmoplegia in which autopsy was performed, and his case was bilateral. The case of Sahlgren and Hofman-Bang[8] which has been interpreted as indicating a lesion *contralateral* to the medial rectus palsy showed at autopsy bilateral lesions. As a matter of fact the most conspicuous lesion was on the *same* side as the more involved medial rectus! Two cases of unilateral internuclear palsy studied anatomically showed unequivocal lesions of the *ipsilateral* medial longitudinal fasciculus.[9,10]

Animal experimentation has led to contradictory conclusions regarding laterality. Stimulation of the medial longitudinal fasciculus in the monkey[11] usually resulted in adduction of the contralateral eye, but destruction of the medial longitudinal fasciculus in the cat[12] resulted in palsies of the homolateral medial rectus.

In summary, the nomenclature being employed should be stipulated. In this paper all of the cases are of the Lutz anterior type (e.g., the defective muscle is the *medial* rectus and not the externus) with one possible exception (Case 35). This series, however, includes cases of both the anterior and posterior types, according to the modified classification. The presence or absence of convergence in each case is listed. The second point to be stressed is that it is important to state whether the internuclear palsy is unilateral, asymmetric, or bilateral. In the unilateral cases the side of the internuclear palsy is designated by the side of the paretic medial rectus. For example, in a *right* unilateral internuclear palsy dextroversion is normally performed, but the right eye lags on levoversion, although the right medial rectus may function normally on convergence. Monocular nystagmus characteristically occurs in the abducting, or left, eye in this instance.

Case Material

This study is based on 58 cases of internuclear ophthalmoplegia, all of whom were seen by one of us. There are 29 unilateral and 29 bilateral cases. These are clinically of different significance and will be treated separately. The records of 70 cases were reviewed, but only 58 had sufficient data to be included in the present series. A letter requesting follow-up information was written to each patient, and in cases where this was not obtained, a request was made to the Bureau of Vital Statistics to see if the person were living or dead. The cases were then analyzed for the following points: unilateral or bilateral involvement, age, sex, side affected, presence or absence of convergence, skew deviation, vertical nystagmus, trigeminal nerve involvement, duration of symptoms, long motor tract signs, long sensory tract signs, plantar reflexes, total follow-up, mortality, time from diagnosis to death in the cases who died, cerebrospinal fluid findings, visual fields, cranial nerve involvement, cerebellar signs, diplopia, speech, abdominal reflexes, deep tendon reflexes, blood pressure, pupils, duration of the internuclear ophthalmoplegia, and clinical impressions. These findings are presented for the most part as follows: (1) general findings (Table 1), (2) ophthalmologic findings (Table 4), and (3) neurologic findings (Table 5).

TABLE 1.—*General Findings in Internuclear Ophthalmoplegia*

	Unilateral	Bilateral
Sex		
Men	17	14
Women	12	15
Age, yr.		
Lowest	5	19
Oldest	71	60
Average	47.8	38.2
Side involved (unilateral cases)		
Right	20	
Left	9	
Duration of symptoms at time of diagnosis		
1 Day-1 wk	12	3
1-4 Wk	6	2
1-3 Mo.	2	2
3-12 Mo.	3	4
1-5 Yr.	4	9
5-10 Yr.	1	5
Over 10 yr.	1	4
Time from diagnosis to death in deceased cases		
0-3 Mo.	4	0
3-6 Mo.	0	0
6-12 Mo.	1	0
1-5 Yr.	3	2
5-10 Yr.	0	3
Over 10 yr.	0	1
Total deceased	8	6
Total follow-up		
0-3 Mo.	7	1
3-6 Mo.	0	1
6-12 Mo.	5	2
1-5 Yr.	8	9
5-10 Yr.	3	9
Over 10 yr.	1	5
None	5	2
Average	25.1 mo.	78.3 mo.
Blood pressure		
Over 140/90	13	0
Average systolic	172 mm. Hg	
Average diastolic (average of 13 hypertensive cases)	96	

Table 1 reveals an essentially equal sex incidence in the bilateral cases, although men are slightly in the majority (59%) in the unilateral cases. The unilateral cases averaged 10 years older than the bilateral cases. About 40% of the unilateral group were hypertensive (blood pressure over 140/90), whereas none of the bilateral group had a significant blood pressure elevation. These factors (commoner in men, older age group, and occurrence of hypertension) are consistent with the reported[9] higher incidence of vascular disease in the unilateral group.

Diagnoses.—A diagnosis of multiple sclerosis was made by the Neurology Division of the Massachusetts General Hospital in 28 of the bilateral cases. It should be noted that in each instance this diagnosis was based on other clinical findings than simply the ocular status. One patient had tabes dorsalis. Another patient with a clinical diagnosis of multiple sclerosis had concomitant Hodgkin's disease proved by biopsy. Thus, in 96% of the bilateral cases, a clinical impression of multiple sclerosis was made.

The high incidence of vascular disease previously noted[9] in unilateral cases was confirmed in this study. The diagnoses in the 29 unilateral internuclear palsies were as follows:

Basilar artery disease	13
Multiple sclerosis	5
Diabetes mellitus	4
Lupus erythematosus disseminata	1
Wernicke's syndrome	1
Encephalitis	1
Glioblastoma multiforme	1
Vascular lesion	1
Hypertensive vascular disease	2
	29

Two patients of the group with basilar artery disease had concomitant diabetes. If one groups the cases of basilar artery disease, disseminated lupus, hypertension, diabetes mellitus, and vascular lesion together, 18 of 29, or 67%, of the group had a vascular basis for the internuclear palsy. Four of the 29, or 14%, had diabetes mellitus.

Mortality.—Of the unilateral cases, 8 are known to be dead, 11 are known to be alive, and the status of 10 is unknown at this time. Of those with definitive information, 42% are dead. Autopsies were performed in five of the eight unilateral cases which died. In but two of these was special attention directed to the brain stem. Both revealed lesions in the medial longitudinal fasciculus ipsilateral to the internuclear palsy.[9,10] In an additional case, a glioma was verified by biopsy. Thus, in six of the eight unilateral cases which died, the cause

TABLE 2.—*Histologically Proved Cases of Unilateral Internuclear Ophthalmoplegia*

Case No.	Duration of Life from Onset of Disease Process	Duration of Life from Diagnosis of INO	Autopsy Diagnosis
10	6½ mo.	2 wk.	Disseminated lupus
13	5 yr.	5 yr.	Diabetes mellitus; multiple cerebral thromboses
17	1 yr.	12 wk.	Basilar aneurysm
18	2 yr.	4 days	Basilar aneurysm
26	12 mo.	9 mo.	Glioblastoma multiforme (craniotomy & biopsy)
50	8 wk.	7 wk.	Malignant nephrosclerosis

of death was substantiated by histologic study. These were as shown in Table 2.

Of the *bilateral* cases, 6 are deceased, 11 are alive, and the status of 12 is unknown at this time. Of the bilateral group with current information, 35% are dead. None of the six bilateral cases that died were autopsied in this hospital, but their course had been typical of advanced multiple sclerosis over a period of many years in each instance. It should be noted that many of the cases about which current information is lacking were followed for some time before being lost to follow-up. This factor will be brought out later.

Skew Deviation.—Table 4 reveals some interesting facets about the eye status of these patients. One point of interest is that in the 12 cases of unilateral internuclear ophthalmoplegia with skew deviation, the eye ipsilateral to the lesion was *hypertropic* in 10. In one case, the side of the skew was not stipulated. In the other patient, a unilateral paralysis of vertical gaze was present in the opposite eye. This is in contrast to the statement in the literature that usually in skew deviation the eye on the side of the lesion is *hypotropic*.[5]

Visual Fields.—Three of the unilateral cases had visual field defects. There were two cases of left homonymous hemianopia and one instance of an upper altitudinal defect in one eye attributed to retrobulbar neuritis. Four of the bilateral cases had visual field defects. Two patients presented bilateral central scotomata, one had a left lower quadrantanopia, and one presented a uniocular upper temporal defect, which was attributed to retrobulbar neuritis. None of the unilateral cases had impairment of visual acuity due to retrobulbar neuritis at the time of the internuclear palsy. One interesting patient, however, had a unilateral internuclear ophthalmoplegia, which subsided spontaneously, and after six symptomless years had a profound retrobulbar neuritis in one eye, which again cleared. A clinical diagnosis of multiple sclerosis had been made at the first episode. It is noted that two of the bilateral cases are legally blind in both eyes from optic neuritis (7%).

Pupils.—The pupils were usually not impaired significantly in these patients. Aniso-

TABLE 3.—*Follow-Up Data from Cases of Internuclear Ophthalmoplegia*

	Unilateral				Bilateral			
	INO				INO			
	Present	Absent	Not Followed	Died	Present	Absent	Not Followed	Died
1-3 Mo.	3	5	9	5	0	5	5*	0†
3-12 Mo.	2	1		1	2	3		0
1-5 Yr.	2	2		1	6	2		2
5-10 Yr.	1	0		1	3	0		2
Over 10 yr.					3	0		2
				8				6

* These five cases with bilateral internuclear palsies died at 18, 45, 84, 90, and 14 months after diagnosis. Four of them had the internuclear palsy still present when they were lost to follow-up. In one patient the palsy had cleared at 4 mo., but the patient died at 45 mo.

† One of the five cases with no follow-up of the internuclear palsy died somewhat more than 10 years after the diagnosis had been made.

TABLE 4.—*Ophthalmologic Findings in Internuclear Ophthalmoplegia*

	Unilateral	Bilateral
Convergence		
Present	19 (83%)	19 (80%)
Absent	4	6
No comment	6	4
Skew deviation		
Present	12 (43%)	2 (13%)
Absent	11	14
No comment	6	13
Vertical nystagmus		
Present	14 (54%)	20 (74%)
Absent	10	5
Parinaud's syndrome	2	2
No comment	3	2
Vision		
20/20-20/40	17	20
20/50-20/100	3	2
20/200 or Less	1 (cortical blindness)	2 (both had bilateral optic neuritis)
"Normal"	2	2
Not given	6	6
	29	29
Visual fields		
Quantitative perimetry	12	13
Confrontation fields	12	4
No comment	5	12
Field defects	3 (12%)	4 (24%)
Diplopia		
Present	20 (74%)	15 (63%)
Absent	7	9
No comment	2	3
Pupils		
Normal	16 (60%)	19 (86%)
Abnormal	9	3
No comment	4	7

coria was noted in nine patients with unilateral internuclear palsies. The clinical diagnosis of Horner's syndrome was made in only one patient, who had a basilar aneurysm at autopsy. This is of interest in connection with the statement that Horner's syndrome is a rarity in multiple sclerosis.[13]

Tigeminal Nerve Involvement.—An unexpected finding in this study was the high incidence of trigeminal nerve involvement in internuclear ophthalmoplegia. Eight of the unilateral cases had paresthesias in trigeminal distribution, which were usually around the mouth and lips on either side. Perioral paresthesias have been stressed [14] as a symptom in basilar artery disease. Only one of the unilateral cases had frank trigeminal pain, however. On the other hand, 10 of the bilateral cases had trigeminal neuralgia, and several of these eventually required alcohol injections and/or trigeminal rhizotomy for relief. Only three of the bilateral cases complained of paresthesias in trigeminal distribution. The trigeminal neuralgia in the bilateral cases was not always present at the time the internuclear palsy was diagnosed. Pain and numbness in the face, shoulder, and neck were noted in several records of patients with bilateral internuclear palsies. At times neck flexion was associated with variation in severity of facial paresthesiae, and whether or not this represented a symptom analogous to Lhermitte's sign in spinal cord disease could not be ascertained. It is known that 4% of patients with trigeminal neuralgia will develop multiple sclerosis.[15] However, a 5% incidence of trigeminal neuralgia in unilateral internuclear palsy stood in striking contrast to the 59% incidence noted in the bilateral cases of this series.

Plantar Reflexes.—Two points concerning plantar reflexes are of interest. Bilateral Babinski reflexes were present in 2 of 20 unilateral cases (10%) and in 10 of 22 bilateral cases (45%), at the time of diagnosis of the internuclear palsy. Secondly, six of the unilateral cases had unilateral Babinski responses. It should be noted that the upgoing toe was contralateral to the internuclear palsy in five patients and ipsilateral in only one. This clinical observation appears to reinforce the suggestion that the medial longitudinal fasciculus lesion is ipsilateral to the involved eye, as such a lesion would be above the pyramidal decussation.

Other Cranial Nerve Involvement.—A final point in Table 5 of interest is that of associated cranial nerve involvement. In order of frequency, in the *unilateral* internuclear palsies, cranial nerves involved were V, VII, conjugate gaze palsy, VIII, VI, X, III, II, and IX. In the *bilateral* cases, cranial nerves were involved in the following order of frequency: V, VII, II, conjugate gaze palsy, VIII, X, III, and IV. Conjugate gaze palsies occurred in 20% of the unilateral cases but in only 7% of the bilateral cases.

TABLE 5.—*Neurologic Findings in Internuclear Ophthalmoplegia*

	Unilateral	Bilateral
Trigeminal symptoms		
Paresthesias	8 (44%)	3 (18%)
Trigeminal neuralgia	1 (5%)	10 (59%)
No V symptoms	9	4
No comment	11	12
Long motor tract signs		
Present	9 (33%)	10 (45%)
Absent	18	12
No comment	2	7
Long sensory tract signs		
Present	8 (33%)	8 (33%)
Absent	16	16
No comment	5	5
Plantar reflexes		
Both plantars down	14	9
Both plantars up	2	10
Right plantar up	2	0
Left plantar up	4	3
Not given	7	7
	29	29
Spinal fluid protein		
Recorded	13	20
Lowest	23 mg. %	16 mg. %
Highest	84 mg. %	124 mg. %
Average	47.1 mg. %	47.2 mg. %
Spinal fluid colloidal gold curve		
Negative curve	1	4
First zone curve	0	1
Midzonal curve	7	12
First and midzone	2	4
Cerebellar signs		
Present	10 (52%)	15 (68%)
Absent	9	7
No comment	10	7
Speech		
Normal	7	4
Slurred	3 (30%)	15 (79%)
No comment	19	10
Abdominal reflexes		
Intact	11	3
Absent	6 (35%)	14 (82%)
No comment	12	12
Deep tendon reflexes		
Normal	16	12
Abnormal	9 (36%)	10 (45%)
No comment	4	7
Cranial nerves		
I	0	0
II	1	3
III	1	1
IV	0	1
V	9	13
VI	3	2
VII	6	3
VIII	4	2
IX	1	0
X	2	1
XI	0	0
XII	0	0
Conjugate gaze palsy	6	2

Comment

Bilateral internuclear ophthalmoplegia has been considered [6] pathognomonic of multiple sclerosis. This was the diagnosis in 28 of 29 bilateral cases in this series. One patient with a bilateral internuclear palsy had tabes dorsalis with a positive history of syphilis and positive serologic tests on both peripheral blood and spinal fluid. As no histologic diagnosis was obtained in this patient, whether or not he had both central nervous system syphilis and multiple sclerosis as well cannot be determined. The occurrence of a bilateral internuclear palsy in a patient with a clinical diagnosis of multiple sclerosis, who later had abdominal Hodgkin's disease proved by biopsy, raised the question of the possibility of progressive multifocal leukoencephalopathy [16] in this patient. The patient is still alive. It is seen that with only these two possible exceptions, the presence of a bilateral internuclear ophthalmoplegia is in essence diagnostic of multiple sclerosis.

Unilateral internuclear ophthalmoplegia, on the other hand, presents a more diverse pathogenesis. Vascular disease of the basilar-vertebral arterial system is the commonest cause of this lesion. Two main groups of unilateral cases were seen: younger patients, who had angiomas, congenital aneurysms, or collagen vascular disease, and older patients, with generalized arteriosclerosis and atheromatous disease of the basilar system, frequently with hypertension, and at times with diabetes mellitus.

The prognosis of internuclear ophthalmoplegia is seen to be quite variable and depends on the cause. One patient had a bilateral internuclear palsy in 1942, which subsided within three months, and he now writes that he has enjoyed good health in the ensuing 16 years without other neurologic symptoms! Some others, however, had rapid progression of disease.

The frequent occurrence of symptoms involving the descending nucleus of the trigeminal nerve as well as central type seventh nerve palsies with bilateral internuclear palsies suggests that the medial longitudinal fasciculus involvement occurs at a pontine level. The high incidence of trigeminal neuralgia in the bilateral cases

TABLE 6.—*Summary of Internuclear Ophthalmoplegia*

	Unilateral	Bilateral
Sex	Men more than women 6:4	Equal sex incidence
Age	Older	Younger
Onset	Often abrupt	Often gradual
Skew deviation	Not infrequently present; ipsilateral eye usually up	Rarely present
Vertical nystagmus	Present in 54%	Present in 74%
Diplopia	Present 74%	Present in 63%
Blood pressure	Occasional hypertension	No hypertension
Trigeminal paresthesias	Present in 44%	Present in 18%
Trigeminal neuralgia	Present in 5%	Present in 59%
Long motor tract signs	Present in 33%	Present in 45%
Long sensory tract signs	Present in 33%	Present in 33%
Bilateral Babinski response	Present in 10%	Present in 45%
Spinal fluid protein	Normal	Normal
Colloidal gold curve	Midzonal	Midzonal
Cerebellar signs	Present in 52%	Present in 68%
Abdominal reflexes	Absent in 35%	Absent in 82%
Cranial nerve involvement	V, VII, conjugate gaze palsy, VIII, VI, X, III, II, IX	V, VII, II, conjugate gaze palsy, VIII, X, III, IV
Conjugate gaze palsy	Present in 20%	Present in 7%
Prognosis	Of 19 with current information, 5 (24%) died within 1 yr.; 50% of cases who died, died within 3 mo.; av. from diagnosis to death in cases who died: 19 mo.; internuclear palsy cleared in 20% within 3 mo.	Of 17 with current information, none (0%) died within 1 yr.; av. from diagnosis to death in cases who died: 83 mo. internuclear palsy cleared in 25% within 3 mo.
Cause	Vascular (67%)	Multiple sclerosis (96%)

is of definite interest. Paton [3] had pointed out that the posterior longitudinal bundle is said also to link up with the sensory nucleus of the fifth nerve.

Further studies of this interesting syndrome are needed to answer many unsolved problems. Cases of the Lutz posterior type of internuclear ophthalmoplegia, substantiated by caloric labyrinthine stimulation, should be published if seen. Further anatomic studies of internuclear ophthalmoplegia are needed. The location of the lesion in skew deviation in particular merits further anatomic study. The response to anticoagulant therapy in the unilateral cases should be evaluated.

Summary

The unilateral and bilateral forms of internuclear ophthalmoplegia are relatively distinct entities.

Unilateral internuclear ophthalmoplegia occurs more frequently in men and at any age but most often in the older age group. It typically involves the right side and lasts only a few weeks but may last for years. It is apt to occur in patients with hypertension or diabetes and appears to be due to a vascular lesion in the pons. While the medial rectus is paralyzed on conjugate gaze, its function is usually preserved for convergence. Vertical nystagmus is frequent but not constant. Skew deviation is frequent. The commoner neurologic signs associated with unilateral internuclear ophthalmoplegia are transient cerebellar signs and dizziness at onset. Trigeminal paresthesias are often present around the mouth and lips on either side. The fifth and seventh cranial nerves are the most frequently involved in these patients, and conjugate gaze paresis occurs occasionally. The internuclear palsy may clear completely, but four patients in this series died within two months of developing this lesion. The prognosis must be guarded.

Bilateral internuclear ophthalmoplegia occurs in men and women equally. Any age may be affected. Bilateral involvement is almost invariably indicative of multiple sclerosis. Vertical nystagmus is usually present on upward gaze. Unlike the unilateral variety, skew deviation is infrequent in the bilateral cases. The commoner neurologic signs associated with bilateral internuclear ophthalmoplegia are trigeminal neuralgia, long motor tract signs, frequently bilateral Babinski responses, cerebellar signs, scanning speech, and absent abdominal reflexes. Not all of these signs are present at time of onset of the internuclear palsy, however, but develop at some time during the course of the illness, as is expected in

multiple sclerosis. The prognosis in these cases is as unpredictable as is multiple sclerosis in general. As the syndrome may clear and no further evidences of multiple sclerosis may ensue for years, this may be pointed out to the patient. On the other hand, of six patients with bilateral internuclear palsies who died, death occurred at an average of 83 months after the internuclear palsy had been first noted (range, 18-144 months).

The main differences between the unilateral and bilateral cases are presented in Table 6.

243 Charles St. (14).

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Syndrome of Nonsyphilitic Interstitial Keratitis and Vestibuloauditory Symptoms

A Long-Term Follow-Up

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In 1945 and 1949, one of us (D. G. C.) described eight patients who presented a syndrome consisting of a characteristic type of interstitial keratitis associated with vestibuloauditory symptoms which usually result in complete deafness.[1,2] The ocular signs consist of patchy deep corneal infiltrates which tend to fluctuate in intensity and distribution, are usually located in the periphery, and are accompanied by deep corneal vascularization if they persist long enough. The vestibuloauditory symptoms consist of simultaneous onset of vertigo, tinnitus, and deafness. These usually progress rapidly to complete nerve deafness and nonresponsive labyrinths. Either the ocular or the vestibuloauditory system may be affected first, but the other is involved within two months. Young adults are peculiarly susceptible. The syndrome is always accompanied by leukocytosis and occasionally by eosinophilia. No evidence of syphilitic infection has been found.

The purpose of this paper is to report a long-term follow-up of patients with this syndrome. The study was undertaken with the specific aim of following the suggestion in the literature that this syndrome was a manifestation of polyarteritis nodosa,[3-5] temporal arteritis,[6] or postvaccinal involvement.[7] It was also planned to obtain information on the eventual outcome of the disease.

The material consists of follow-up of six of the eight previously reported cases. Seven additional cases, seen by us or reported to us by colleagues,* are included. All the patients have been followed for a minimum period of two and one-half years.

Observations

The period of follow-up, sex, age at onset, and evidence of associated systemic disease before, during, or since the onset of the syndrome are listed in the Table. The cases are arranged according to the duration of follow-up.

There have been 2 deaths in the 13 cases studied. Unfortunately, no autopsies were obtained. Except for residual visual and auditory defects, the first of these patients (Case 13) was apparently well until a few days before death. Cough, blood-stained sputum, chest pain, fever, and evidence of pneumonitis developed, and she died after two days. The second patient (Case 10) had had rheumatic fever with aortic insufficiency and cardiac enlargement starting two years before the onset of the ocular and auditory symptoms. Two weeks before death this patient became tired and developed pain in the abdomen, vomiting, and an enlarged liver. He subsequently became jaundiced and dyspneic and is said to have died "in peripheral vaso-motor collapse."

In only 2 of the 11 remaining cases have all the signs and symptoms been confined to

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Case Data

Case No.	Sex	Age, Yr.	Follow-Up Period, Yr.	Evidence of Systemic Disease Before or During Acute Illness	Subsequent Development of Systemic Disease
1	F	24	14	None	Hypertension, mild
2	F	30	14	None	None
3	M	35	13	General malaise	None
4	M	30	12	None	None
5	F	22	9	None	Developed "spastic colitis"
6	F	19	9	None	Hypertension, severe
7	F	31	8	Chills, fever, muscle pains, retinal artery occlusion	Hypertension, severe
8	F	21	6	Muscle pain & fever 1 yr. prior to onset	None
9	M	24	4	None	15 mo. later developed thrombosis posterior inferior cerebellar artery, arthralgia, hyperglobulinemia, cardiomegaly
10	M	24	3	Rheumatic fever, 2 yr. prior to illness, with aortic insufficiency	Died in cardiac failure with jaundice
11	M	28	2½	Muscle pain, migrating polyarthritis, abdominal cramps, numbness of legs, colitis, & "glandular fever"	None
12	F	31	2¾	Fever, severe headache, abdominal distress, occlusion superior branch central retinal artery with orbital edema	None
13	F	22	1	None	Died of acute lobar pneumonia

the ocular and vestibuloauditory systems. Three of the patients have developed hypertension, two of a severe degree. Three of the patients (Cases 9, 11, 12) had such diffuse evidence of systemic disease that they were considered to have polyarteritis, but this could not be confirmed by biopsy. One of these patients (Case 11) was so ill that death was thought to be imminent, yet he made a dramatic recovery.

In these cases a wide variety of therapeutic agents, including broad-spectrum antibiotics and adrenal corticosteroids, have been tried without beneficial effect.

Of the 11 surviving patients, only one has severe visual loss in both eyes. Ocular examinations of five show normal findings, and four have normal visual function with residual scarring and vascularization of the cornea. Two patients have evidence of previous occlusive vascular disease of the retina with secondary optic atrophy. In both of these patients, the arterial occlusion occurred during the acute phase of their illness.

Of the 13 patients, all but two were deaf or had severe hearing loss. There was an associated loss of labyrinthine function.

Since the original reports, the Treponema pallidum-immobilization test for syphilis has become available. Three of the original cases with corneal changes indistinguishable from classical syphilitic interstitial keratitis have been shown to have a negative test.

Comment

Nothing has been uncovered to enlighten us as to the etiology of this curious syndrome. Its suggested relationship to polyarteritis remains speculative. Certainly, these cases have not run the usual course of polyarteritis. We cannot draw any conclusions from the obscure relationship between the acute syndrome and the two deaths. Only 1 of the 13 patients had been vaccinated in the few months preceding onset of the vestibulo-ocular disease.

The facts that one patient developed cardiac enlargement of undetermined etiology, that three had evidence of occlusive vascular disease, and that three have developed hypertension certainly lead one to believe that the oculoauditory portion is only one phase of a systemic disturbance related to the cardiovascular system. Only continued follow-up and a larger series may confirm this suspicion.

Once the disease has clearly subsided, there is no evidence that the ocular symp-

toms will reappear. The over-all prognosis for vision and probably for life is good, but once deafness occurs, the prospect for return of hearing is poor.

Summary

Thirteen patients with the syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms have been followed from 2½ to 14 years. The etiology remains obscure, and there is no effective therapy. Two patients have died without contributing further to our knowledge. Six patients have manifested evidence of systemic cardiovascular disease. The prognosis for life and vision is good, for hearing, poor.

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Staining of the Retina with Saccharated Iron Oxide

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Introduction

This study deals with retinal flat preparations and histological sections of eyes stained with saccharated iron oxide. In contradistinction to many other routinely employed staining techniques, the method presented here has shown its greatest merits when applied to the nonfixed tissue and, therefore, has produced its best results in vital or supravital specimens.

The use of saccharated iron oxide (hereinafter SIO) is facilitated by the availability of commercial preparations for systemic administration of iron.* In principle, the SIO stain is related to Hale's [1] colloidal iron stain and its modification by Rinehart and Abul-Haj.[2] The latter technique has recently been applied to the eye by Zimmerman [3,4] for demonstration of acid mucopolysaccharides (AMS) in formalin-fixed and paraffin-embedded sections. For the purpose of comparison, Zimmerman's approach has been compared in this study with other metachromatic staining techniques, such as Steedman's [5] Alcian Blue 8 G*. With both methods, the AMS are stained blue. The specificity of all these staining techniques for AMS, however, is somewhat uncertain and requires control staining of duplicate sections pretreated with hyaluronidase (Wydase, Wyeth) or other AMS-specific enzymes. In this study, only hyaluronidase was employed. In addition, a few retinal flat preparations and cross sections were also stained with periodic acid-Schiff (PAS) (Glick [6] and McMannus [7,8]) according to the modification worked out by Becker in the laboratory of Friedenwald [9] for the demonstration of vascular changes in diabetic retinopathy.[10-12]

It is interesting that Weed and Wegefarth,[13] in 1914, and Berens and Posner,[14] in 1932, employed similar techniques in their excellent studies on the circulation of the intraocular fluid. Both groups of investigators observed in cross sections that an aqueous solution of iron ammonium citrate and potassium ferrocyanide, when injected into the vitreous body, diffused into the perivascular spaces of the retina. Berens and Posner,[14] in addition, found iron in the perivascular tissue of the blood vessels in the optic nerve. The implications of such studies as well as of related experiments performed in our laboratory will be discussed elsewhere. The present study is confined to the technical aspects of staining the blood vessels and other tissue components in flat preparations and cross sections of the retina.

Material

For most of the vital and supravital staining of the retina, the eyes of adult albino rabbits were employed. They were supplemented by a moderate number of eyes enucleated from healthy dogs and cats.

For application of SIO to the retina, postmortem rabbit, cat, dog, and some human autopsy eyes were used.

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* Imferon (Bengers, Ltd.), Ferrivenin (Bengers, Ltd.), and Proferrin (Merck, Sharp & Dohme). The latter was used in this study. It is a dark brown liquid which contains 20 mg. of elemental iron per cubic centimeter at a pH of 10.8.

Methods

A. Staining of Flat Preparations of the Retina.—I. Vital Staining with SIO: 1. Injection of 0.1 ml. of a 0.2% iron-containing solution of SIO into the vitreous body of the living animal was performed, with use of No. 26-gauge needle under visual control by indirect ophthalmoscopy. The needle entered the eyeball from the temporal side slightly anterior to the equator. The injections were made when the needle tip approached the posterior half of the retina.

2. Enucleation of the eyes was performed after a given time varying from five minutes to several hours or, in selected cases, from several weeks to months.

3. Immediately after the enucleation, the anterior half of the eyeball was removed and the vitreous body detached from the retina. With the retina still in place, the specimen was briefly rinsed with a 0.9% saline solution and subsequently immersed for 10 minutes into a 4% formaldehyde solution without buffer.

4. The fixative was removed by rinsing with tap water for a few minutes.

5. The specimen was immersed in a mixture of equal parts of 10% hydrochloric acid and potassium ferrocyanide. The freshly prepared solution was applied for at least five minutes bringing forth the dark blue pattern of the blood vessels against a faintly blue background (positive Perls', or Prussian blue, reaction).

6. The stained specimens were washed with water and immersed into a 70% alcohol solution for 10 minutes. Thereafter, the retina was loosened and detached from the underlying layers and the insertion at the optic nerve severed with the help of a spatulum and scissors. The optic nerve was separately cut off from the sclera and longitudinally split into two parts. The staining of the blood vessels in the optic nerve was carried out by the same method as applied to the retina.

7. The separated retina was subsequently placed for about 10 minutes into a 90% alcohol solution, absolute alcohol, and, finally, for about three minutes into xylene. The dehydrated retina was mounted on a glass slide with gum dammar.

The two parts of the optic nerve were subjected to a similar treatment and mounted on a slide with the cutting surfaces pointing toward the cover slip.

II. Supravital Staining: Immediately after the enucleation, SIO solutions varying from 0.5 to 1.5 cc. were injected into the vitreous body, where they remained for a given time. An equivalent amount of vitreous commonly escaped through the opening made for the injection. The rest of the procedure was the same as outlined above.

III. Staining of Fixed Flat Preparations: Fixation of the enucleated eyeball was carried out in a 4% formaldehyde solution without buffer. Washing of the specimen in running water was followed by injection of the SIO solution and work-up as outlined above.

Counterstaining with PAS[6] or with Biebrich scarlet was performed in selected cases. It produced a red or pink background and somewhat improved the appearance of the specimens without contributing essential features.

B. Staining of Histological Sections.—1. Eyes exposed to intravitreal SIO in vivo or supravitally for a period ranging from minutes to several months were fixed in a 4% formaldehyde solution, then embedded in paraffin for sectioning, and stained with Gomori's technique[15] for the presence of iron deposits.

2. Hyaluronidase solutions containing 150 units (Wydase) were applied to duplicate eyes at various time intervals (up to 24 hours) either prior to or after the exposure to SIO.

3. Cross sections of normal eyes fixed in formalin and embedded in paraffin were exposed to a 2% solution of SIO for a period of about 10 minutes, then rinsed with water, and subsequently exposed to a freshly prepared mixture of Perls' reagents. The rest of the procedure was similar to that of Rhinehart and Abul-Haj.[2]

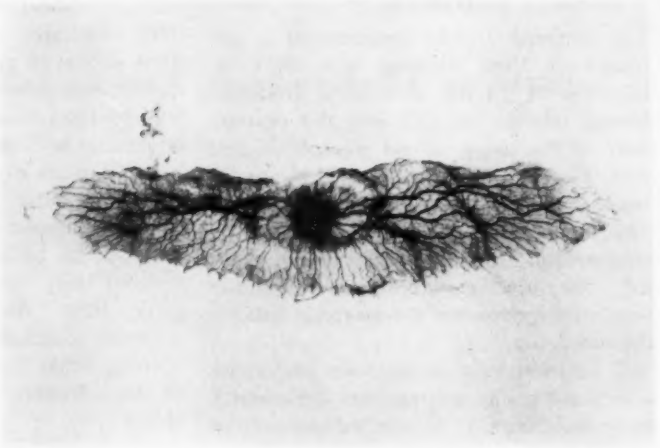

Fig. 1. — Vascular pattern over medullated wings of a rabbit retina elicited by injection of a 0.2% elemental iron-containing solution of saccharated iron oxide (SIO) into the vitreous body one hour prior to death and subsequent exposure to Pearls' reagents yielding a Prussian blue reaction in the perivascular tissue.

Results

With the technique as outlined above, the vital staining of flat preparations and cross sections of the retina yielded very satisfactory demonstrations of the vascular tree, particularly in rabbits. In Figures 1 to 4, the vessel pattern over the medullated wings of the normal rabbit retina is demonstrated. In these animals the SIO solution was injected into the vitreous body in vivo or immediately after death. The structures stained are the internal limiting membrane of the retina and the perivascular tissue, provided the exposure to SIO was confined to a few hours. A complete staining of the entire vessel tree could usually be achieved within 30 to 60 minutes. Within these time intervals no other retinal structures exhibited a positive Perls' reaction with the exception of traumatized areas, such as the location where the needle was introduced for the purpose of the injection of the SIO solution. At this site, some ganglion cells, nerve fibers, and nuclei of bipolar cells, and eventually a few members and nuclei of injured receptors also displayed a posi-

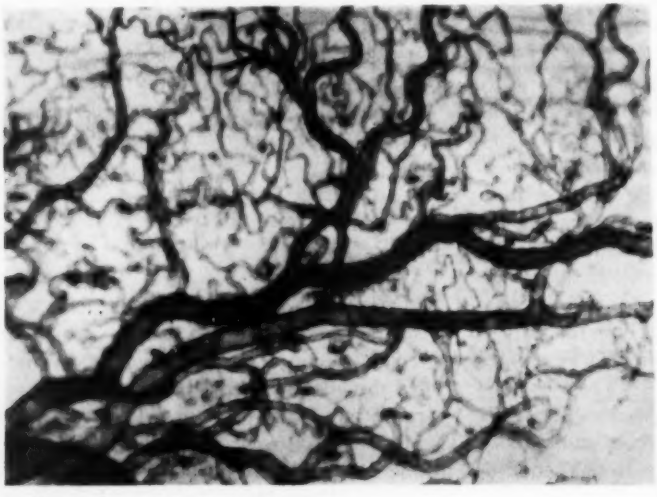

Fig. 2.—The same as Figure 1. Blood vessels from an area close to the optic disc.

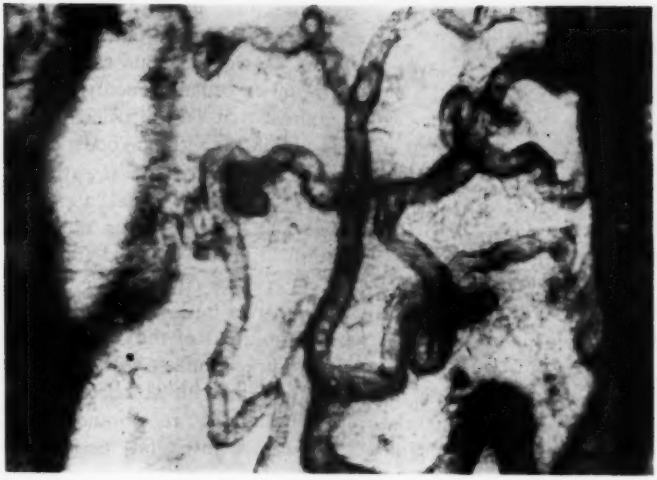

Fig. 3.—The same as Figure 1. Enlarged presentation of capillary loops resembling aneurysms.

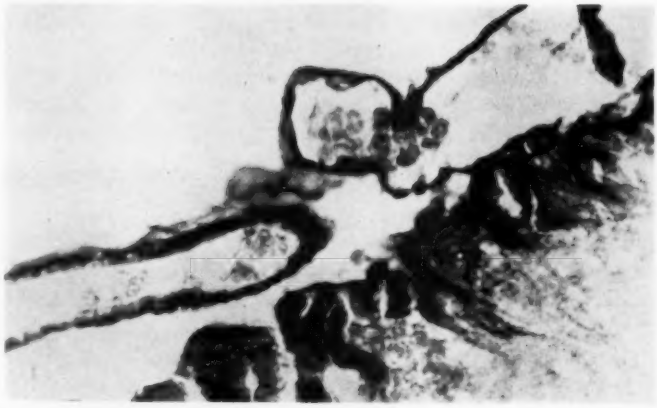

Fig. 4. — Cross section of the retina of an albino rabbit. Positive Perls' reaction of the perivascular and prepapillary tissue due to exposure to SIO for 15 minutes by injection into the vitreous body immediately after enucleation. Negative Perls' reaction in the arterial walls and endothelium, positive reaction in all layers of the veins.

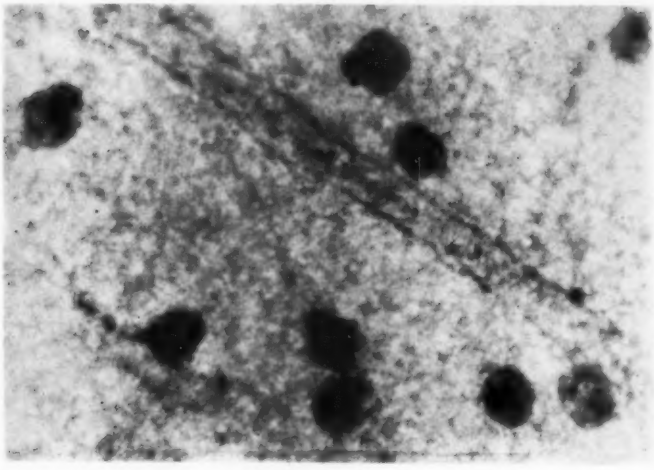

Fig. 5.—Flat preparation of the retina of a dog. Injection of SIO was given one and one-half hours after enucleation. The preparation of the retina was performed eight hours after the injection. Note positive Perls' reaction of the blood vessels and some ganglion cells.

tive iron reaction. The presence of a basement membrane was not elucidated in the rabbit specimens stained in this fashion.

Prolonged exposure of the retina to the SIO solution in the vitreous body resulted in intensification of the perivascular stain and eventually its extension into the vessel wall and the endothelium. If the vital stain with SIO in the vitreous body proceeded for more than 24 hours, ganglion cells and nerve fibers also displayed a positive Perls' reaction. In such cases, however, signs of retinal degeneration were found. In the supravital experiments such changes in the neural elements of the retina were observed even after eight hours' exposure to SIO (Figures 5 and 6). The discussion of these late changes and their implications will be the subject of a subsequent study of the entire complex of siderogenous changes in the retina and other ocular structures.

It is of interest that the diffusion of the iron solution within the vitreous body seems to be facilitated in a direction toward the optic nerve. At the disc, the vessels appeared particularly densely stained. From there the SIO apparently diffused toward the periphery via the perivascular tissue. Consequently, a positive Perls' reaction could also be observed in areas of the retina which had not been in direct contact with the SIO as can be inferred from the absence of iron in the internal limiting membrane. The likelihood of such a diffusion mechanism

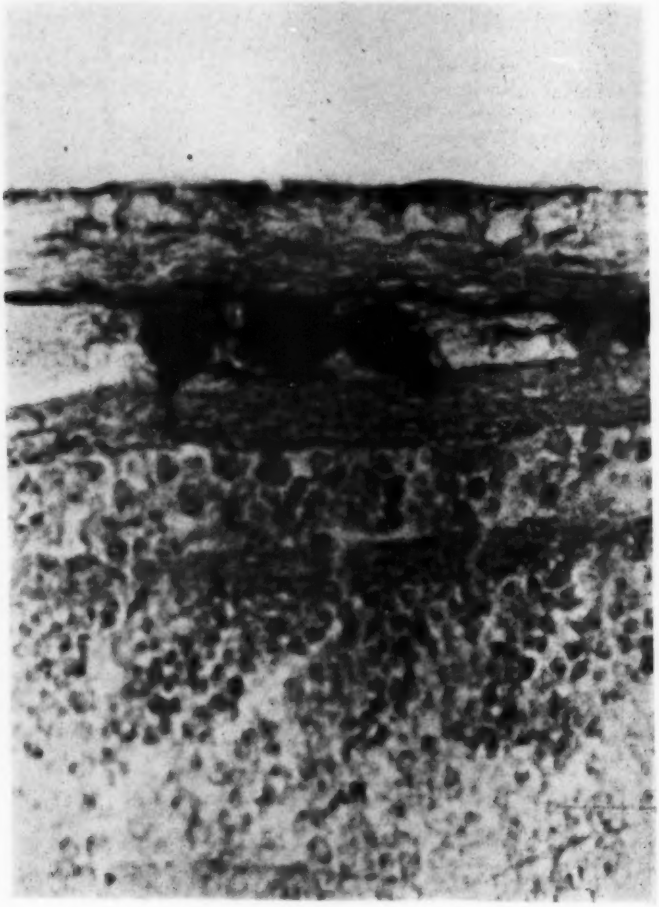

Fig. 6. — Cross section of the retina of the same dog as in Figure 5 (other eye) showing positive Perls' reaction of ganglion cells and nerve fibers after exposure to SIO as outlined above.

Fig. 7. — Flat preparation of dog retina, SIO in vitreous body for 24 hours prior to death. Positive Perls' reaction in contracted vitreous body and perivascular tissue of the circularly arranged blood vessels at the optic disc. Radial branches of smaller caliber at right.

was supported by flat preparations of the retina of dogs which had been exposed to SIO in the vitreous body in vivo or supravitally. Figure 7 illustrates the heavy staining of the axial portion of the vitreous body with its insertion at the optic disc, where it fused into the perivascular tissue of the blood vessels. There the vessels form an irregular ring around the optic disc with radial branches leading to the periphery of the retina. However, even in the 24-hour specimens, the blood vessels of the dog retina do not stain as intensively as those of the rabbit retina exposed to SIO for only one hour. Such a species difference in the staining behavior can be explained by the fact that the vessels of the rabbit retina are partly or completely surrounded by condensed vitreous body particularly in the vicinity of the optic nerve. This, of course, is not the case in the human and canine retinae where the blood vessels run in the nerve fiber layer and, therefore, require a longer time to stain. Figure 8 depicts the blood vessels and some ganglion cells with positive Perls' reaction in the retina of an adult dog, 24 hours after injection of SIO into the vitreous body. Figure 9 refers to

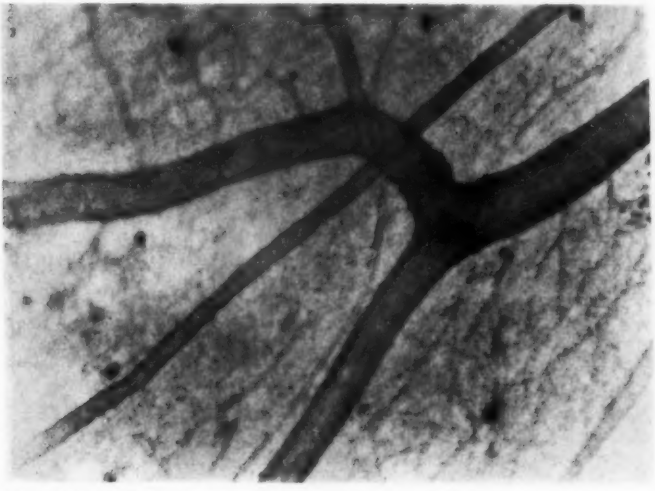

Fig. 8. — Flat preparation of dog retina exposed to SIO in vivo for 24 hours. Note positive Perls' reaction in some ganglion cells.

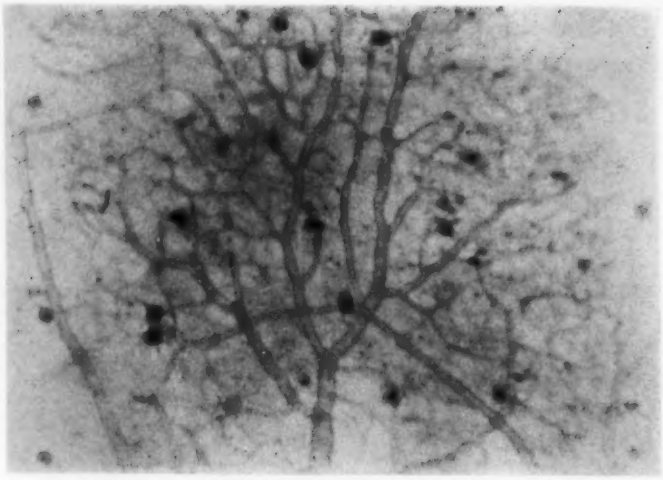

Fig. 9. — Flat preparation of the retina of the same dog showing terminal branches in the periphery of the retina.

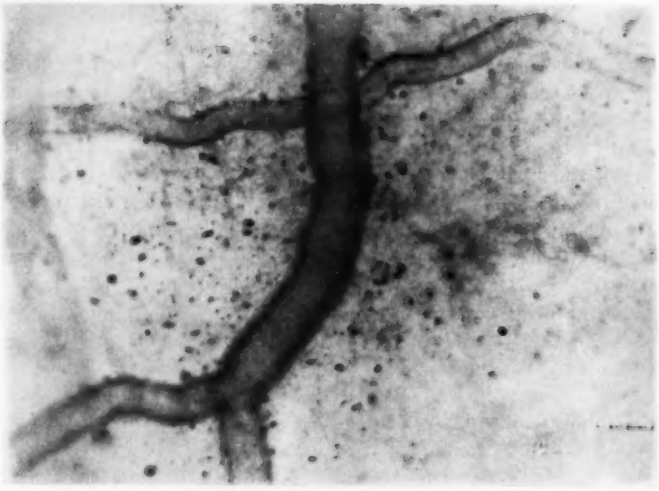

Fig. 10.—Human retina, flat preparation exposed to SIO for four hours, five days after death. Positive Perls' reaction of perivascular tissue and vessel walls. Cellular elements with larger nuclei appear to be ganglion cells, those with smaller nuclei are not defined.

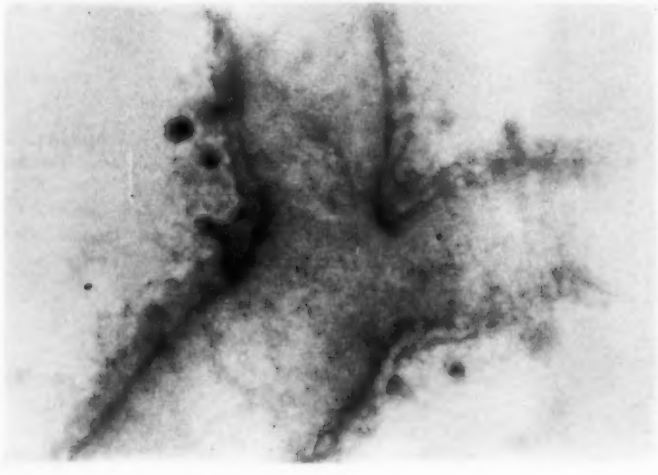

Fig. 11.—The same as Figure 10. Bifurcation of a branch of the central retinal vein showing constriction at the junction.

terminal branches of peripheral retinal vessels of the same dog.

Particularly interesting is the fact that the blood vessels in the dog retina as well as in human eyes (Figures 10 and 11) when stained with SIO showed some indication of a basement membrane similar to that described by Friedenwald[9] in the PAS-stained flat preparations. However, there was a great variation in its stainability, even in specimens of one and the same species. In some instances, the basement membrane appeared stained more lightly than the vessel wall. In other instances, just the opposite was the case. So far, the factors responsible for such inconsistencies have not been assured. The most persistent observation made in this connection is the fact that the basement membrane stained more intensively in postmortem specimens.

Figure 10 is a photograph of a human retina exposed to SIO for four hours, the injection into the vitreous body being performed five days after death. Figure 11 represents a larger magnification of the bifurcation of a retinal vein from the same patient. The constriction of vessels at junctions is a common finding, much as observed in the living eye.

A striking illustration of the intricate relationship between the internal limiting membrane, the perivascular tissue, and the wall of the central retinal vein in the vicinity of the optic nerve of a dog eye is demonstrated in Figure 12. In this animal, the injection of the SIO solution into the vitreous body was carried out two hours after death. Over a period of eight hours after the injection, the SIO molecules diffused into the perivascular tissue and gradually penetrated the entire vessel wall, eliciting a dark blue staining reaction after exposure to Perls' reagents. At the left of Figure 12, one can see the separation of the perivascular tissue from the medial layer resulting in the formation of a triangular space which is filled out by a soft connective tissue yielding a much weaker positive Perls' reaction. The band-like extensions from the vessel wall taper off to the left and gradually fuse at an acute angle into the internal limiting membrane.

In rabbits, the perivascular tissue is more loosely arranged and, therefore, may render less resistance to diffusion along the vessels into the optic nerve. Figure 13 represents a longitudinal section of the optic nerve from an albino rabbit which received an intravitreal injection of SIO solution about four hours prior to death. A heavy positive Perls' reaction indicated that the SIO had probably migrated along the perivascular tissue throughout the entire length of the optic nerve. It also penetrated into the

Fig. 12.—Main branch of central retinal vein at the optic disc of a dog. Cross section showing positive Perls' reaction of the entire vessel wall. Note separation of the perivascular tissue at the margin of the vessel. The SIO solution was injected into the vitreous body two hours after death and remained in the vitreous for eight hours.

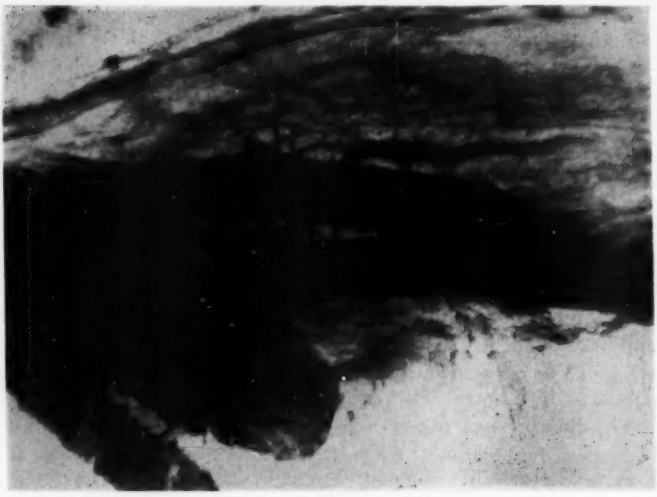

Fig. 13. — Longitudinal section of the optic nerve of an albino rabbit showing positive Perls' reaction of the perivascular tissue and of adherent connections of the septa and tributaries four hours after injection of SIO solution into the vitreous body of the living eye. Parts of the retina and preretinal condensations of vitreous body are visible at left and below.

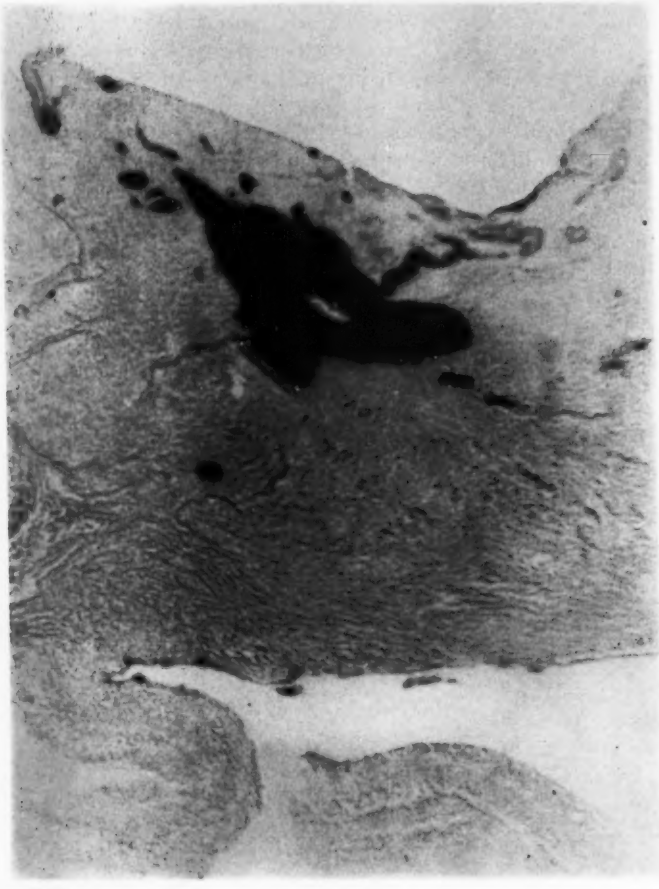

Fig. 14. — Oblique section of the optic nerve close to the disc. Cross section of the central retinal vessels showing a heavy staining for iron of the perivascular tissue eight hours after injection of 0.2 cc. of a 0.2% iron-containing solution of SIO into the vitreous body of the living animal. Gomori's stain.

septa directly connected with the perivascular tissue. Cross sections, as shown in Figure 14, demonstrate how well-delineated the iron concentrated around the main branches and tributaries of the central retinal vessels in the optic nerves of the experimental animals in less than 15 minutes. This confirms the findings made by Berens and Posner.[14]

Finally, it may be of some interest that the SIO stain, if applied to cross sections of formalin-fixed eyes, yielded equally good results as Hale's modification of Rhinehart and Abul-Haj's technique. The metachromatic differentiation of the various tissue constituents is essentially the same with both techniques. Hyaluronidase did alter the staining of the vitreous body but did not impair noticeably the stainability of the retinal perivascular tissue.

Comment

The staining technique described here obviously represents a modification of Hale's technique, although performed with a somewhat different iron compound. The new features of this technique are its application to the living eye for the purpose of staining the blood vessels in flat preparation and cross sections.

In the living eye, the stainability of the vitreous body and of the perivascular tissue in the retina may well depend on the relatively strong affinity of the iron for AMS, since the positive Perls' reaction appeared confined to the acellular constituents of these structures. The AMS in the vitreous body lost its stainability with SIO after the application of hyaluronidase. The perivascular tissue, however, responded little to the enzyme. Prolonged exposure to SIO for days or weeks seemed to result in the break-down of some barriers surrounding the ganglion cells and nerve fibers. Whereas in the living eye 24 hours and more exposure to SIO were needed to elicit a positive Perls' reaction in ganglion cells and nerve fibers, approximately eight hours were found sufficient in the postmortem specimens of dogs and rabbits to render a positive iron reaction. The number of ganglion cells exhibiting a positive iron stain varied with the time elapsed after death and the duration of postmortem exposure to SIO.

The SIO solution in the vitreous body seemed to lack the ability to penetrate the living retina readily even if applied over days or weeks. For that reason, the bacillary layer of the retina did not stain unless the SIO solution had been brought into direct contact with it by subretinal injection, or by diffusion between retina and pigment epithelium at areas of trauma. But even under these conditions, only a relatively small number of rods and their nuclei took up enough iron to yield a positive Perls' reaction in flat preparations or cross sections.

It is beyond the scope of this presentation to speculate about the nature of the tissue reactions involved. From the theoretical viewpoint, there seems to be no doubt that iron can combine with many other tissue constituents besides AMS. It is most likely that the delayed staining reaction for iron as it occurred in the ganglion cells and nerve fibers of our specimens exposed to SIO post mortem or over a longer period in vivo has been produced by a combination of iron with nucleic acids (PO_4-groups) or proteins (COOH-groups) rather than AMS.[16]

On the other hand, the persistency of the intensive reaction in the avascular and protein-deficient vitreous body and in the perivascular tissue of the retinal vessels and optic nerve seems to speak in favor of a linkage of iron with AMS. The iron-linkage to whatever constituent is responsible for the blue stain of the perivascular tissue persists and can be demonstrated after several months.

Summary

A new staining technique for the study of vascular patterns in flat preparations and cross sections of the retina is described. It is based on the vital and supravital affinity of acid mucopolysaccharides (AMS) and

possibly other tissue constituents in the vitreous body and perivascular tissue for iron. Saccharated iron oxide (SIO) was injected into the vitreous body of rabbits and dogs and man either in vivo or immediately after death. The staining constituents of the vitreous body proved to be largely sensitive to hyaluronidase, whereas those in the perivascular tissue resisted hyaluronidase. The best delineation of retinal vessels were achieved in the rabbit.

640 S. Kingshighway (10).

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The Effect of Heparin on the Ocular Tuberculin Reaction

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In a previous communication [1] we confirmed the findings of others [2-4] on the inhibitory effect of heparin on anaphylactic hypersensitivity. The present study was undertaken to explore the role of heparin in the tuberculin type of hypersensitivity, with use of the eye of the rabbit as a convenient site for observing the local reaction elicited by the injection of specific antigen.

Method

Thirty-two normal adult rabbits were infected with a virulent strain of Mycobacterium tuberculosis (var. hominis) by injecting 0.1 ml. of a saline suspension of living organisms into the anterior chamber of the right eyes.

The suspension used for inoculation was standardized so that a 2 mm. platinum loopful, when spread over an area of 1 sq. cm. on a microscope slide, showed an average of 50 organisms per high-power field. The animals developed a progressive tuberculous infection of the inoculated eyes. Three months after infection the animals were skin-tested with 0.005 mg. of purified protein derivative (P. P. D.). The animals were then divided into three approximately equal groups of reactivity on the basis of the skin test.

Group 1 was given an anterior chamber injection into the left eye, consisting of 0.0012 mg. of P. P. D. This group served as the control group.

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From the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital and University.

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Group 2 was given the same amount of P. P. D. as Group 1 and was immediately heparinized by subcutaneous administration of heparin at the rate of 10 mg. of heparin per kilogram of body weight. This dose was repeated at six-hour intervals for a total of 24 hours.

Group 3 was given 0.0012 mg. of P. P. D. and 0.1 mg. of heparin simultaneously into the anterior chamber of the left eye. The technique used for the injections was the same as that described in a previous paper.[1]

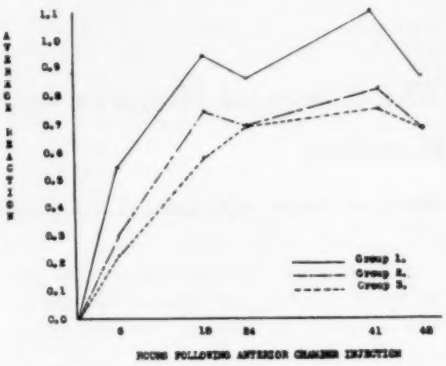
The eyes were examined at 6, 18, 24, 41, 48, and 96 hours after the anterior chamber injection and were graded by the degree of hyperemia and thickening of the iris. Injections were administered to the eyes by one of us, and the examinations made by the other without previous knowledge of which group was under examination. A numerical value was given to each eye according to the reaction observed: Thus, a severe reaction was given the value of 3; a moderate reaction, 2, and a mild reaction, 1. The iris reactions observed in each

TABLE 1.—*Skin Reactions of Groups 1, 2, and 3 to P. P. D. Before Ocular Injections*

Group 1		Group 2		Group 3	
Rabbit No.	Area of Induration, Mm.	Rabbit No.	Area of Induration, Mm.	Rabbit No.	Area of Induration, Mm.
T 1	25	763	25	730	25
T 2	22	T 18	20	T 5	21
T 4	20	702	20	T 24	20
775	20	757	18	762	20
764	19	766	15	769	18
707	18	713	15	768	15
729	15	716	15	759	15
708	12	770	10	712	15
704	10	760	8	T 12	10
714	7	773	5	758	8
706	5			709	5

TABLE 2.—*Iris Reactions of Groups 1, 2, and 3*

Group 1 (Control)							Group 2 (Systemic Heparin)							Group 3 (Local Heparin)						
	Hr. After Injection							Hr. After Injection							Hr. After Injection					
Rabbit No.	6	18	24	41	48	96	Rabbit No.	6	18	24	41	48	96	Rabbit No.	6	18	24	41	48	96
T 1	0.0	1.0	1.0	1.0	1.0	0.0	763	0.5	1.0	0.5	0.5	0.5	0.0	730	0.0	0.5	1.0	1.0	1.0	0.0
T 2	0.5	1.0	0.5	1.0	1.0	0.25								T 5	0.5	0.5	0.5	0.5	0.25	0.0
T 4	1.0	1.5	1.5	1.5	1.0	0.0	T 18	0.0	1.0	1.0	1.0	1.0	0.0	T 24	0.0	0.5	0.5	0.5	0.5	0.25
775	0.5	1.5	1.5	1.0	1.0	0.25	702	0.5	0.5	1.0	1.0	0.5	0.25	762	0.0	0.5	0.5	1.0	1.0	0.0
764	0.0	1.0	0.5	1.0	0.5	0.0	757	0.5	1.5	1.5	1.5	1.0	0.5	769	0.0	0.5	1.0	1.0	1.0	0.25
707	0.5	1.0	0.5	1.0	0.5	0.25	766	0.0	1.0	0.5	1.0	1.0	0.0	768	0.0	0.5	0.5	0.5	0.5	0.0
729	1.0	1.0	1.0	1.0	1.0	0.25	713	0.0	0.0	0.0	0.5	0.5	0.0	759	0.5	1.5	2.0	1.5	1.5	0.25
708	1.5	0.5	0.5	1.0	1.0	0.25	716	0.5	0.0	0.0	0.5	0.5	0.0	712	0.5	0.0	0.0	0.5	0.0	0.0
704	0.5	1.0	1.5	1.5	1.5	1.0	770	0.5	1.0	0.5	0.5	0.5	0.0	T 12	0.5	0.5	0.25	0.25	0.25	0.0
							760	0.5	1.0	1.5	1.5	1.0	0.25	758	0.5	0.5	0.5	1.0	1.0	0.25
714	0.5	0.5	0.5	1.0	0.5	0.0	773	0.0	0.5	0.5	0.25	0.25	0.25	709	0.0	1.0	1.0	0.5	0.5	0.25
706	0.0	0.5	0.5	1.0	0.5	0.25														



Averages of iris reactions of control and heparinized rabbits.

group of rabbits were totaled and the average value determined.

Results

Table 1 shows the skin reactions of the animals to P. P. D. before the injections had been administered. The iris reactions of the three groups of animals at various intervals after the anterior chamber injections are listed in Table 2. The Figure represents in graphic form the average reaction of each of the groups at the various periods of observation.

The control group developed a marked reaction which had reached its peak and had begun to subside at the end of 48 hours.

Group 2, which had been heparinized systemically, showed a less marked reaction which was slower in its development and did not at any time reach the severity of the reaction observed in the control group.

Group 3, which had been given heparin locally into the anterior chamber simultaneously with the P. P. D., showed a less intense reaction which developed even more slowly than in Group 2.

The eye reactions of the three groups subsided gradually, and at the end of 96 hours the reactions were minimal in all groups.

Summary

In the eyes of animals with tuberculin hypersensitivity, heparin inhibits the inflammatory response to the anterior chamber injection of P. P. D.

Heparin exerts an anti-inflammatory action when administered either systemically or locally.

Wilmer Institute, The Johns Hopkins Hospital (5).

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The Lattice Type of Familial Corneal Degeneration

A Histopathologic Study

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Corneal tissue obtained after penetrating keratoplasty from two patients with the rare lattice type of familial corneal degeneration have provided the material for this histopathologic study. Although the clinical and biomicroscopic characteristics of this type of corneal degeneration are well known, only two reports of the histologic changes can be found in the English literature,[1,2] and in one of these [2] the nature of the degeneration remains in doubt.

Some authors [3,4] have contended that all types of familial corneal degeneration are of similar origin, since different forms have been seen in the same family. Furthermore, the histologic picture of the lattice type of corneal dystrophy appears to differ only quantitatively from that of the commoner nodular type. Dimmer,[5] who published his clinical description of this entity in the same year as Haab,[6] prepared a scraping from the cornea of one of his patients and found an amorphous, eosinophilic material which he suspected was either colloid or hyaline. Löwenstein,[7] however, obtained corneal material by keratectomy and was the first to describe the characteristic deposits of an amorphous, sometimes stratified material in the superficial layers of the cornea. He distinguished two types of deposit: an eosinophilic material in front of Bowman's membrane and a basophilic material behind it. The epithelium was very irregular, and Bowman's membrane was defective. These two forms of hyaline deposit can also be distinguished by the May-Gruenwald stain.[8] They are apparently deposited within the stroma after a necrobiosis of the corneal lamellae and seem to be responsible for the linear pattern seen clinically.[1,9]

This same general pattern of pathologic changes was later described by others. Maury [2] found fat in these deposits in an eye enucleated because of endophthalmitis and beginning atrophy after cataract extraction. This finding has not been substantiated by subsequent investigators, and the corneal degeneration in this patient may not have been of the familial type.

The possible association of the clinically visible lines with the corneal nerves has been discussed repeatedly. Löwenstein [7] originally observed that the degenerative changes in the cornea appeared to follow the course of the corneal nerves. While other authors [9] have disagreed with this hypothesis, Vrabec,[11] by the use of special strains, has recently demonstrated degenerative changes in the nerve fibers of the superficial cornea. The presence of corneal anesthesia in some patients and episodes of pain during the course of the disease in others tend to confirm these findings.

Report of Cases

CASE 1.—A 58-year-old white man was admitted to the Veterans Administration Hospital in Philadelphia on May 15, 1957, complaining of gradually decreasing vision in both eyes beginning 10 years previously. His paternal grandfather, his father, two uncles, and one brother were known to have suffered from familial corneal dystrophy

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From the Departments of Ophthalmology, Hospital of the University of Pennsylvania; Veterans Administration Hospital, Philadelphia, and State University of Iowa.

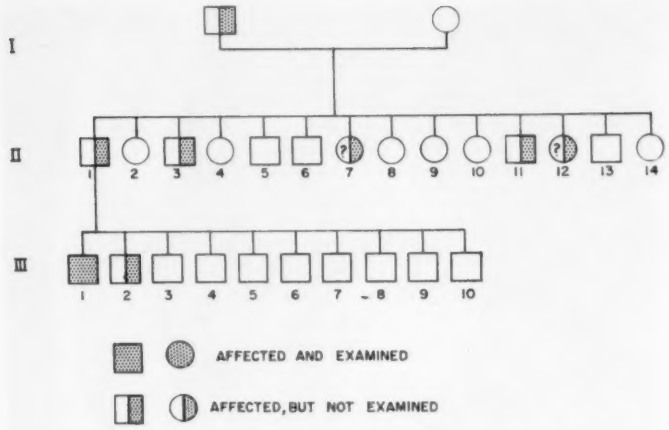

Fig. 1 (Case 1).—Family tree. The patient described is No. 1 in Generation III.

(Fig. 1). His father and two uncles had had successful transplants in one or both eyes. His brother had had a successful transplant in one eye. Two of his father's sisters were known to have had poor vision uncorrected by glasses, but the nature of their disability was not known.

Visual acuity was found to be 6/60 in the right eye and 6/20 in the left eye with correction. External examination was negative except for the presence of fine grayish streaks in both corneas. The eyes were entirely quiet. Slit-lamp examination indicated marked changes in both corneas (Fig. 2). Coursing through the anterior two-thirds of the stroma were numerous irregular grayish branching lines which were not sharply circumscribed. Smaller nodular accumulations of a similar appearance were present between the branching lines and in the subepithelial area. Occasional dense white granules were present within these deposits. Ophthalmoscopic examination was entirely normal except for the slight haziness produced by the changes in the cornea. General physical examination was negative. Laboratory studies were negative except for a 1+ Kolmer test. On May 16, 1957, a penetrating 7 mm. keratoplasty was performed in the right eye, after which recovery was uneventful. Visual acuity on Dec. 1, 1957, was 6/6 in the right eye and 6/20 in the left eye.

Microscopic Description.—The specimen consists of a corneal button. The epithelium is irregular in most areas, and the basal cells are swollen, vacuolated, and of irregular size. In a few small areas, epithelium has been separated from Bowman's membrane by an amorphous substance which stains blue with Masson's stain.

Bowman's membrane is intact and of regular thickness. Throughout the stroma are deposits of an eosinophilic amorphous substance resembling hyaline. This material is found in all layers of the stroma but is most heavily concentrated in the anterior two-thirds. It is of irregular density and appears to be within the stromal fibers, while adjacent fibers are fragmented and irregular. It is faintly basophilic and stains red with Masson's stain (Fig. 3) and orange with Van Gieson's stain (Fig. 4). Descemet's membrane and the endothelium are normal.

Case 2.—This 54-year-old white woman came to the University Hospital of Iowa because of poor vision in both eyes. She had complained of decreased visual acuity since the age of 16 years and had become much worse during the last few years. She complained only of occasional irritation of her eyes. She had been examined previously, in 1939, at which time her vision was O. D., 6/21 and O. S., 6/60.

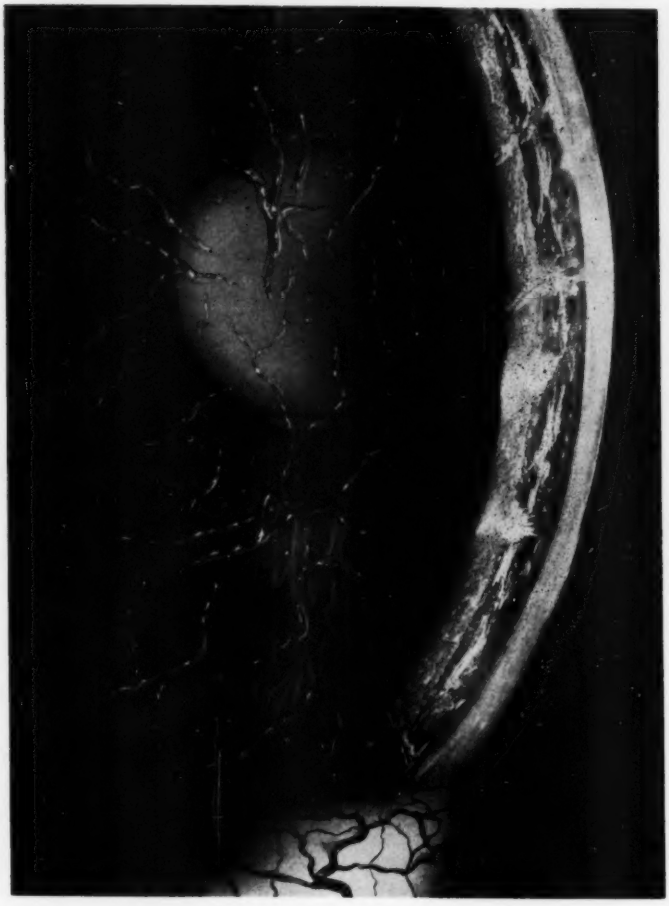

Fig. 2 (Case 1).—Slit-lamp drawing of corneal changes.

Her maternal grandmother and her mother had become blind early in life (Fig. 5). Of her five siblings, two brothers and one sister have poor vision, one brother has good vision, and the eye condition of another brother is unknown. The oldest brother's disability began in his early youth. He had a corneal transplant but lost the eye. The sister has had "milky eyes" since the age of 16. The youngest brother has had visual difficulties since the age of 13. He also had a corneal transplant after which the eye was lost.

Three of the patient's seven children have poor vision. Of these, two could be examined. They showed the typical slit-lamp picture with interlacing lines and tubes in the superficial corneal stroma. The stroma between them and the limbal area was clear. The corneal sensitivity was definitely reduced.

On admission in October, 1957, the patient's vision in both eyes was reduced to counting fingers at 1 ft. Her cornea showed the picture of an advanced reticular degeneration. Only the marginal zone near the limbus was clear. The reticular pattern was still recognizable in the peripheral portions of the cornea, while the central portion was diffusely gray and opaque except for a few nodules. The corneal sensitivity was reduced. On Oct. 8, 1957, a penetrating

Fig. 3 (Case 1).—Stromal deposits, showing hyaline nodules at all levels. Masson's trichrome stain; × 130.

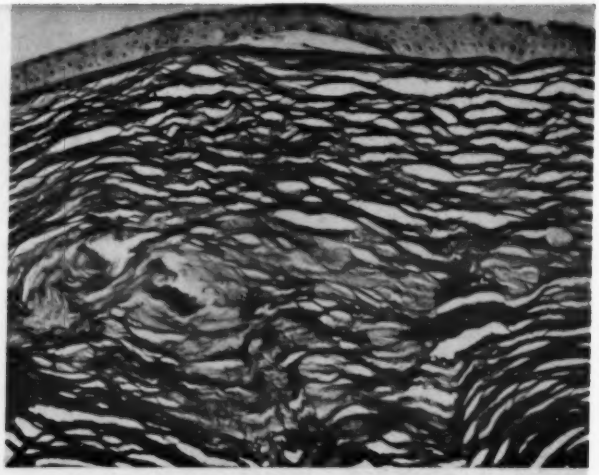

Fig. 4 (Case 1).—Stromal deposits, showing fragmentation of corneal lamellae. Van Gieson stain; × 130.

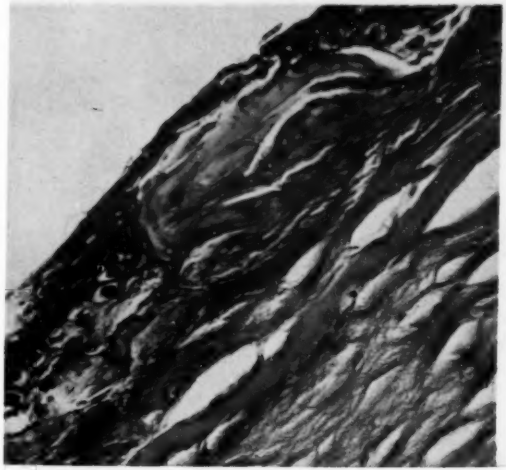

Fig. 6 (Case 2).—Subepithelial deposits. Bowman's membrane is destroyed. Mallory stain; × 305.

Fig. 7 (Case 2).—Subepithelial deposits. Van Gieson stain; × 305.

Fig. 5 (Case 2).—Family tree. The patient described is No. 4 in Generation III.

corneal transplant was performed on the left side. The postoperative course was uneventful.

Microscopic Description.—The specimen consists of a corneal button with sharp outlines. The corneal epithelium is very irregular. It is generally much thinner than normal, often only one layer thick, and in a few places is absent. The epithelial cells do not show their normal regular features, nor are they arranged in the usual layers. Most of the basal cells are round and vacuolated.

Between the epithelium and Bowman's membrane lies a foreign, amorphous substance. This granular material encroaches upon the epithelium and lies occasionally within the epithelial cells. In some areas an individual epithelial cell is filled with this eosinophilic material. The nucleus is still visible in some cells, while it has disappeared in others. The material stains yellow with Mallory (Fig. 6), orange with Van Gieson (Fig. 7), and blue with Masson's stain. It does not stain with the Weigert or periodic acid-Schiff stains. In a few areas near the periphery of the button the deposits are calcified (Fig. 8). The subepithelial plaques of hyaline are of variable thickness, usually about one-half that of the normal epithelium. In a few areas they replace the entire epithelium, while in others they are thinner than Bowman's membrane. Bowman's membrane is wavy but continuous, and only in the areas of peripheral calcification can a few defects be found.

The stroma shows a loose arrangement of the fiber bundles. There are no inflammatory cells or vessels present. Toward the periphery of the corneal button are a number of amorphous deposits. These are oval or round and of variable size. The material is eosinophilic and stains blue with Mallory, red with Masson, and orange with the Van Gieson stain. The deposits are of variable size and can be found in all layers of the stroma. Descemet's membrane and the endothelium are normal.

Comment

The changes observed histologically in the corneas we have studied appear to confirm in most respects the findings of previous authors. Hyaline-like deposits were found in the subepithelial region and within the stroma in both eyes. In one eye the findings were predominantly subepithelial, while in the other they were predominantly stromal. In both patients, the deposits were arranged in linear as well as nodular fashion, distinguishing this type of dystrophy from the granular form of familial corneal degeneration of Groenouw. In all other respects,

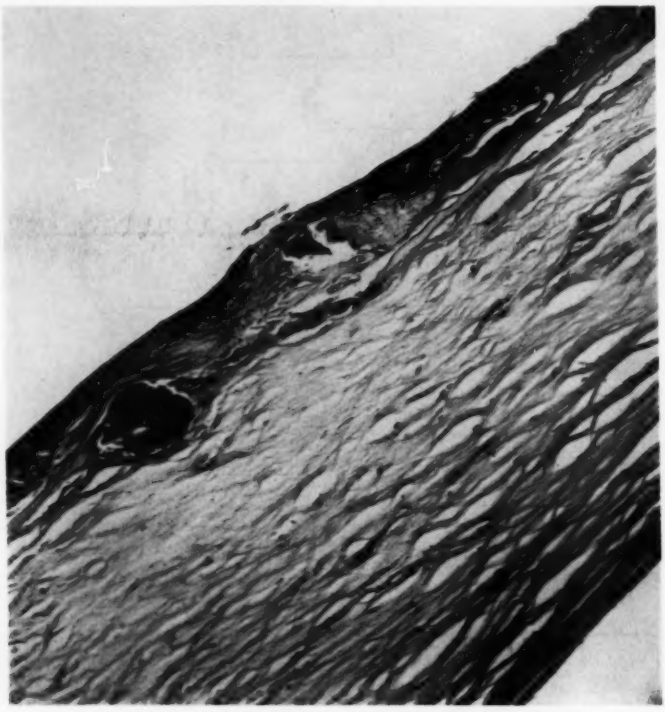

Fig. 8 (Case 2).—Photomicrograph of calcified deposits; × 132.

these changes were similar to those described by other authors in the nodular type. It is interesting to note that these two deposits vary in their staining reactions and are obviously of different chemical structure.

One unusual feature in Case 2 was the presence of calcium within the subepithelial nodules. No association with corneal nerves was demonstrated in these specimens.

Summary

Two corneas from patients with the rare lattice type of familial corneal degeneration have been studied histologically. Although this condition differs from the granular type of familial dystrophy in its clinical appearance, the histologic findings are similar in both types. Subepithelial and stromal hyaline-like deposits, differing in their staining characteristics, are found in both forms of dystrophy. The difference in the appearance of the two eyes reported emphasizes the variability previously described by others.

313 S. 17th St. (3).

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Dependence of Aqueous-Blood Sugar Ratios on Method of Determination

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Considerable variation is seen in ophthalmic literature concerning sugar concentration ratios of aqueous humor to whole blood and aqueous humor to blood plasma. These variations may be caused, in part, either by differences in sugar levels of different species of animals studied, or because animals were given a general anesthetic before sugar samples were withdrawn, or because adequate samples were not taken to justify a conclusion. The greatest variable, however, appears to be in the blood sugar method that has been used to make the determinations.

The majority of investigators have found that the sugar levels in plasma were higher than in aqueous humor,[1-7] but there was a rather marked variation in aqueous-blood ratios found by these investigators. Furthermore, Kirby and Wiener [8] found a higher level of dextrose in whole blood of human beings than in the aqueous humor. Aqueous and plasma sugar levels, however, have been described as being similar in the rabbit and horse,[9,10] although Walker [11] observed that three out of five rabbits had higher aqueous than plasma glucose levels.

The present study was undertaken in order to ascertain how dependent the sugar levels in blood and aqueous were on the method of determination.

Material and Methods

Rabbits of the California, Duchess, and New Zealand white strains have been used in this experiment. They were not fasted and were placed in an air-conditioned room (76 F) at least 24 hrs. before any studies were made. Blood was withdrawn from the marginal ear vein into a heparinized centrifuge tube. Samples of this blood were used for sugar determinations. The remaining blood was cooled and centrifuged for plasma sugar determination. After topical tetracaine (Pontocaine) anesthesia, aqueous was withdrawn through an anterior chamber puncture.

The sugar content of whole blood, plasma, and aqueous humor from each animal was analyzed by two of five methods. Part of each specimen was analyzed for sugar by the Nelson-Somogyi technique.[12-13] Sugar was determined in the other part of the specimen by one of four methods, anthrone,[14] Glucostat (glucose oxidase reagent),[15] * Folin-Malmros,[16] or Hagedorn-Jensen.[17]

Glucose oxidase (DeeO) † was added to some of the samples of the protein-free filtrate used in the Nelson-Somogyi technique. These samples were incubated for one and one-half hours at 37 C. Glucose oxidase per se could not be used with the anthrone, Hagedorn-Jensen, or Folin-Malmros techniques because of changes produced in the color reactions.

Several methods were used in the statistical analysis of the data. 1. The mean and standard errors were determined for the blood aqueous and plasma sugar values obtained by each method. 2. A Type I analysis of variance (Lindquist) [18] was

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From the Department of Anatomy, State University of Iowa College of Medicine.

The statistical analysis was made by Dr. Paul Blommers and the Statistical Service of the State University of Iowa.

* Supplied by Worthington Biochemical Corp., Freehold, N. J. Contains glucose oxidase, peroxidase, and *o*-dianisidine.

† Takamine Laboratory, Clifton, N. J.

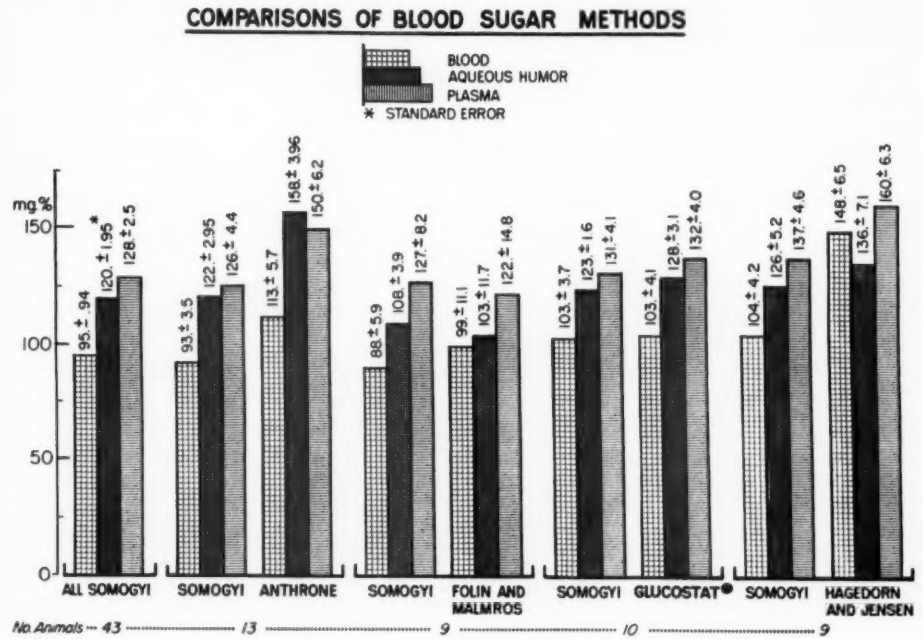
carried out using independent random samples of animals for each method of sugar determination. The determinations were made with three materials (aqueous, blood, and plasma) by each method. This analysis provides a statistical test of the significance of the differences among the means for each method over all materials and among the means for each material over all methods. It also provides a test of the significance of the interaction ‡ between methods and materials. Finally, if the presence of a significant interaction justifies such efforts, this analysis makes possible tests of significance of simple effects, that is, of differences among methods means considered separately for each material and of differences among material means considered separately for each method. 3. Analyses of variance [18] were carried out with four factorial designs. In each such design the three materials comprised one factor. The second factor (methods) always involved determinations derived by the Nelson-Somogyi technique in comparison with determinations derived by one of the other four techniques. The animals constituted the remaining factor: each animal contributed six determinations, one for each of the two methods in conjunction with each of the three materials.

Five per cent was adopted as the critical level of significance. However, most differences reported as significant were so beyond a 1% level.

‡ The extent to which differences among methods means vary from material to material.

Results

There was considerable variation in the blood and aqueous sugar levels in the rabbit when different methods of determination were used (Figure). Since the sugar levels for each animal were determined by two procedures, i. e., Nelson-Somogyi and by one of the other four methods, it was possible to make comparisons between each of the four methods and the Nelson-Somogyi technique. When sugar values for blood, aqueous, and plasma were averaged for each method, the anthrone and Hagedorn-Jensen groups had higher values than the



Nelson-Somogyi groups. On the other hand, the Folin-Malmros and Glucostat sugar levels were similar to their respective Nelson-Somogyi determinations.

Consideration of the standard errors for the average blood, aqueous, and plasma sugar levels gave some clue as to the reliability of the data. The highest standard error was found in the Folin-Malmros group, and the second highest was in the Hagedorn-Jensen group.

In addition to the actual values obtained for the sugar in the blood, aqueous, and plasma, the ratios of aqueous-blood and aqueous-plasma were determined and are shown in Table 1. These ratios were not analyzed statistically, since the raw data have been considered in this respect. As would be expected, a wide variation was noted in the ratios of results between the different methods as well as between the different methods and the Nelson-Somogyi technique. The lowest values for the ratios of aqueous-blood were obtained for the Hagedorn-Jensen and Folin-Malmros methods and the highest value for the anthrone procedure. The Nelson-Somogyi and Glucostat methods gave similar values.

TABLE 1.—*Ratios of Sugar Values, Aqueous-Blood, and Aqueous-Plasma*

Method	No. Animals	Ratios	
		Aqueous-blood	Aqueous-plasma
All Nelson-Somogyi	43	1.26	0.94
Nelson-Somogyi	13	1.31	0.97
Anthrone		1.40	1.05
Nelson-Somogyi	9	1.23	0.85
Folin-Malmros		1.04	0.84
Nelson-Somogyi	10	1.19	0.94
Glucostat		1.24	0.97
Nelson-Somogyi	9	1.21	0.92
Hagedorn-Jensen		0.92	0.85

Less variation was seen in the aqueous-plasma ratios. The lowest ratio was found when the Folin-Malmros method was used, but the ratios for the Nelson-Somogyi determinations of the same animals and for the rabbits used in Hagedorn-Jensen series were very similar. The highest value was obtained with the anthrone technique, and in this instance the aqueous sugar levels were higher than those for the plasma.

The total reducing substances have been considered as simple sugars. However, the sugar values obtained by the Glucostat and the Nelson-Somogyi methods probably represent "true" glucose. The reaction of the Glucostat method is based on the aerobic oxidation of glucose catalyzed by glucose oxidase. Hydrogen peroxide is released which reacts with a chromogenic acceptor, *o*-dianisidine. In the case of the Nelson-Somogyi method, the protein-free filtrate was treated in many instances with glucose oxidase. This treatment removed glucose from the solution, and the reducing substances left were negligible, i. e., from 0 to 5 mg. %. Consequently, since "true" glucose is determined by the Glucostat and Nelson-Somogyi methods, these methods have been used for comparing the other procedures in the statistical analysis.

The results of the Type I (Lindquist) analysis were considered first. In this instance, the Glucostat method was viewed as the criterion method, that is, as the method against which, or with reference to

TABLE 2.—*Type I Design: Table of Means*

Materials Related	Nelson-Somogyi	Anthrone	Glucostat	Hagedorn-Jensen	Folin-Malmros	Total
Aqueous humor	119.7000	157.5000	126.3750	140.0000	96.5714	129.5000
	(*N*=10)	(*N*=10)	(*N*=8)	(*N*=7)	(*N*=7)	(*N*=42)
Blood	95.4000	111.5000	101.2500	152.7143	92.0000	109.3333
	(*N*=10)	(*N*=10)	(*N*=8)	(*N*=7)	(*N*=7)	(*N*=42)
Plasma	126.2000	149.6000	129.1250	157.4286	114.7143	135.6190
	(*N*=10)	(*N*=10)	(*N*=8)	(*N*=7)	(*N*=7)	(*N*=42)
Total	113.7667	139.5333	118.9167	150.0476	101.0952	
	(*N*=30)	(*N*=30)	(*N*=24)	(*N*=21)	(*N*=21)	

TABLE 3.—*Summary of Type I Analysis of Variance* *

Source	*d. f.*	*m. s.*	*F*
Among animals	41		
Methods	4	9,045.34	11.16 †
Error	37	810.78	
Within animals	84		
Materials	2	7,945.53	82.40 †
Meth. × mat.	8	1,051.79	10.91 †
Error	74	96.42	
Total	125		

* *d. f.*=degrees of freedom: *m. s.*=mean squares, or variance; *F*=variance ratio.
† Significant.

which, the other methods were to be compared. The mean determinations are shown in Table 2 and a summary of the analysis of variance in Table 3. Considered collectively, the over-all methods means (bottom margin of Table 2) differed significantly. When individual comparisons were made between the over-all mean Glucostat determination and the over-all means for each of the other methods, all differences were significant except for the Nelson-Somogyi method. Over-all materials means (right-hand margin of Table 2) differed significantly when considered collectively and also when considered by individual pairs. The significant interaction between methods and materials indicated real variation in the differences among methods means from material to material. Consequently the differences among methods means were studied separately for each of the three materials. In the case of aqueous (Row 1, Table 2), neither the Nelson-Somogyi or Hagedorn-Jensen mean determinations differed significantly from the mean Glucostat determination. However, the Nelson-Somogyi and Hagedorn-Jensen determinations did differ significantly from each other. Agreement between the Nelson-Somogyi and Glucostat determinations was much closer than that between the Hagedorn-Jensen and Glucostat determinations. With whole blood (Row 2, Table 2) the Nelson-Somogyi, anthrone, and Folin-Malmros mean determinations did not differ significantly from the Glucostat determination. Again the Nelson-Somogyi determination was in closer agreement with the Glucostat determination than was that of either of the other methods. The Nelson-Somogyi determination differed significantly from the anthrone determination but not from the Folin-Malmros determination. Finally, when plasma was used (Row 3, Table 2) no significant differences were found among the Nelson-Somogyi, Folin-Malmros, and Glucostat determinations. Agreement was again closest between the Nelson-Somogyi and Glucostat determinations. Thus the Nelson-Somogyi method is the one method which yields results in closest agreement with Glucostat for all materials, considered individually as well as collectively. It is recognized that failure to uncover significant differences is not in any sense a proof that one method is better than another. On the other hand, neither is a hypothesis of the equivalence of such methods refuted, as is the case in those instances in which significant differences were observed.

In the factorial design analysis the Nelson-Somogyi method as compared with one of the other methods provided one factor. The other factors were materials and animals. The analysis was repeated four times, once with each of the four other methods, one independent sample of animals being employed for each analysis. The over-all means for the methods for each analysis are shown in Table 4. The four analyses of variance are summarized in Table 5. Determinations yielded by the anthrone and Hagedorn-Jensen methods differed significantly from those based upon the Nelson-Somogyi method, whereas those derived

TABLE 4.—*Over-All Methods Means for Each Factorial Design Analysis*

Comparison Method	Mean for Nelson-Somogyi	Mean for Comparison Method
Anthrone	114.2	140.1
Glucostat	119.0	120.9
Hagedorn-Jensen	123.1	148.5
Folin-Malmros	108.3	108.5

TABLE 5.—*Summary of the Four Factorial Design Analyses of Variance Involving a Comparison of the Nelson-Somogyi and Each of the Other Methods* *

Source	Anthrone			Glucostat			Hagedorn-Jensen			Folin-Malmros		
	d. f.	*m. s.*	*F*	*d. f.*	*m. s.*	*F*	*d. f.*	*m. s.*	*F*	*d. f.*	*m. s.*	*F*
Methods	1	13,786.78	100.24 †	1	58.02	0.61	1	8,740.17	26.52 †	1	0.67	0.00 +
Materials	2	11,105.63	120.84 †	2	4,746.20	38.26	2	2,579.02	13.88 †	2	4,251.69	24.33 †
Animals	12	1,273.07		9	362.80		8	954.82		8	4,083.91	
Meth. × mat.	2	461.63	17.90 †	2	24.87	0.79	2	1,382.72	21.60 †	2	384.06	5.63 †
Meth. × anim.	12	137.53		9	96.24		8	329.58		8	885.17	
Mat. × anim.	24	91.91		18	124.05		16	185.85		16	174.75	
Meth. × mat. × anim.	24	25.79		18	31.44		16	64.01		16	68.24	
Total	77			59			53			53		

* *d. f.* = degrees of freedom; *m. s.* = mean squares, or variance; *F* = variance ratio.
† Significant.

from the Glucostat and Folin-Malmros methods did not. The over-all means for materials are not shown, but these differences were all significant and of much the same order of magnitude as reported in the case of the Type I analysis.

Comment

There are several important considerations which must be thought of when choosing a particular micromethod for glucose determinations. One of major importance is whether a particular method gives "true" glucose values. Another is whether nonglucose material, either in normal or pathological subjects, gives false glucose readings, and, lastly, how involved or difficult is a particular method.

The anthrone method gives higher readings for sugar than the Nelson-Somogyi method in the present studies, and similar observations have been reported by other workers.[19] Furthermore, although the anthrone procedure is not difficult, it does not separate glucose from other carbohydrates. Durham et al.[14] have pointed out how easy it is to get false readings with the anthrone method because of possible contaminants. From these observations it would have to be concluded that the anthrone method is not very selective in determining glucose.

In the present study the Folin-Malmros technique was carried out using the recommended tungstic acid filtrate. Although the mean values for sugar were similar by the Folin-Malmros to those obtained by the Nelson-Somogyi technique, the standard error for the former method was the largest encountered in any of the methods used in this study. It was pointed out by Somogyi,[20] in 1930, that the tungstate filtrate does not remove as many nonfermentable reducing substances as the zinc filtrate. In 1945, this author noted that copper reagents are preferred because they oxidize sugars more selectively than ferricyanide solutions. Thus it appears that more modern sugar methods are superior to those using a tungstate filtrate and ferricyanide solutions.

The Hagedorn-Jansen method yields high values for blood sugar. The original method called for a protein-free filtrate prepared from NaOH and $ZnSO_4$. Somogyi[21] has shown, however, that NaOH fails to remove all the protein. Protein in turn would reduce ferricyanide, as would glucose. Zipf and Waldo[22] have observed that noncarbohydrate reducing substances in the blood are chiefly glutathione, ergothioneine, uric acid, creatinine, creatine, and ascorbic acid. NaOH apparently does not remove these substances as well as $Ba(OH)_2$.

It appears that the Nelson-Somogyi and Glucostat methods give the most accurate values for glucose of any of the methods studied. The Glucostat method is based on the specific oxidation of glucose by glucose oxidase. When the protein-free filtrate used in the Nelson-Somogyi method is treated first with glucose oxidase the reduction of copper is practically nil, i. e.,

readings equivalent to 0-5 mg. % were obtained. Recently Huggett and Nixon,[15] using reagents the same as those contained in Glucostat, found that blood sugar readings for this method were similar to those obtained with the Nelson-Somogyi technique. On the other hand, the same filtrate gave higher readings for the Hagedorn-Jensen method.

The statistical analysis gives additional information as to the dependability and suitability of the five sugar methods. When the Type I design was used to determine the variance of the methods, it was found that the Glucostat and Nelson-Somogyi were not significantly different. This is of considerable importance in that these methods probably give the most reliable data for the determination of glucose per se.

The factorial design analysis does not give a definite evaluation of the methods. When blood, aqueous, and plasma sugars from the same rabbits were determined by the Nelson-Somogyi procedure and by one of the other four methods, it was found that the Nelson-Somogyi, Glucostat, and Folin-Malmros methods were not significantly different. However, because of the large standard error found in determinations carried out by the Folin-Malmros technique and because of other objections given in this discussion, it is felt that the Folin-Malmros method may result in considerable error in the evaluation of glucose levels.

The question arises now as to whether the Nelson-Somogyi or the Glucostat method is the most suitable for glucose determinations. Both methods use $Ba(OH)_2$ and $ZnSO_4$ for the precipitation of protein. The copper reagent used in the Nelson-Somogyi reagent is stable almost indefinitely, while the glucose oxidase used in the Glucostat method may deteriorate in time even if it is stored in the refrigerator. The Glucostat procedure is probably a little easier to carry out, although it is just about as time consuming.

Summary

Nelson-Somogyi, anthrone, Glucostat, Hagedorn-Jensen, and Folin-Malmros techniques have been used to determine the sugar content of normal blood, aqueous, and plasma.

For the determination of glucose in blood, aqueous, and plasma the most accurate methods described herein appear to be the Nelson-Somogyi and Glucostat techniques.

The aqueous-blood and aqueous-plasma sugar ratios reflect, to some extent, the variations which result from the method employed.

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Iridencleisis

Technique and Results in Ninety-Five Consecutive Operations

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An excellent historical review of iris-inclusion operations is given by Allen.[1] Prior to 1900, incarceration of iris, either intentional or accidental, was occasionally noted to have beneficial effect in control of glaucoma. Coccius,* in 1859, observed, "A piece of iris can drain the aqueous to a larger degree than in any other possible way through the cornea." Bader,† in 1881, stated that prolapse of iris in his procedure was a favorable accident; he believed that a conjunctival staphyloma was desirable in that it formed a safety valve for too high tension of the eye. Iris-inclusion operations, however, remained somewhat in disrepute because of the ever-present fear of sympathetic ophthalmia.

An important contribution to the literature was made in 1903, by Herbert.[2] Having noted that accidental incarceration of the iris after iridectomy seemed to yield a more favorable result, he therefore purposely created a small iris prolapse beneath the conjunctiva, usually in association with iridectomy, in 130 cases. He recognized the importance of obtaining a draining fistula resulting in a conjunctival bleb.

The popularity which iridencleisis enjoys today can largely be attributed to the articles of Holth.[3-5] He performed his first subconjunctival iridencleisis in 1904, and in 1922, published an excellent series of photomicrographs demonstrating subconjunctival iris fistulas. Holth's technique involved the use of a stop keratome, penetrating the bulbar conjunctiva approximately 8 mm. from the limbus and creating a subconjunctival tunnel to its entrance in the sclera 1.5 to 2 mm. from the limbus. The scleral incision measured 6 mm. in length. The iris was grasped with forceps near the edge of the pupil and pulled outward so that the pupillary border was just outside the limbal incision. A meridional cut was made through the iris, with the pillars falling onto the scleral surface. The conjunctival incision was then closed. Holth advocated the use of iridencleisis in both acute and chronic glaucoma. He reported that 50% of his patients were permanently controlled without miotics. In an additional 35% of the cases, miotics were required for only about six months postoperatively and the remaining 15% could usually be controlled on continued miotics without further surgery.

Holst[6] and Gjessing[7] both reported large series of iridencleisis in which Holth's technique was utilized. Holst stated that the tension was controlled in 91% of his 281 cases (75% without miotics and 16% with miotics). When he also considered cases in which there was decrease in visual acuity or increase in loss of visual field, he stated that an over-all success rate of 79% was obtained. Gjessing, in evaluating 198 cases, reported that the tension was controlled in 144 cases without miotics and in 36 cases with miotics, making up a total of 91% of his cases. After considering cases in which there was increased loss of visual field or decrease in visual acuity, he reported success in 145 of the cases (73%).

The fear of sympathetic ophthalmia after iridencleisis appears to be largely unfounded

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* Quoted in Allen.[1]

† Quoted in Allen.[1]

in the light of accumulated clinical experience. In 1954, Mackie and Rubinstein [8] reported a review of the literature in which they listed almost 2,000 iridencleisis (including 110 cases in their series), with sympathetic ophthalmia occurring in only 4 cases, an incidence of approximately 0.2%.

During the past half-century, a number of variations in the technique of iridencleisis have been advocated. Stallard [9] utilizes a 5 mm. incision placed 2 mm. from the limbus. He advocates doing a small cyclodialysis and also creating a small scleral hinge. Rather than making a meridional incision of the iris, he creates a small iris flap without interruption of the iris sphincter. He reports successful control of the tension in 98% of his cases. Mulberger and McDonald [10] have recently reported a series of 62 cases in which the Stallard technique was utilized, with successful control of tension in 94%. Miotics were required in approximately one-half of the cases in which a successful result was obtained.

Weekers and Weekers [11] advocate making the incision into the anterior chamber with a cataract knife, the incision being made in one bold stroke so that a spontaneous iris prolapse is obtained. In their technique, the iris is torn into two fragments which are then incarcerated in the scleral incision. Lundsgaard's modification [12] of the Holth technique involves an *ab externo*, or scratch, incision with a knife rather than a keratome incision. Constantine,[13] utilizing the Lundsgaard modification, reported a series of 107 operations with successful control of tension in 89% of the cases. Goar and Schultz [14] advocate a scratch incision with a keratome, a meridional cut in the iris without iridodialysis, and incarceration of only one pillar. They report tension reduced to normal in 90%, visual acuity decreased in 12%, and visual fields decreased in 11% of the 72 eyes evaluated. Reese [15] has advocated a keratome incision and stresses the importance of performing a small iridodialysis with incarceration of the pillars into each corner of the operative incision with a minimum amount of manipulation.

Mechanism of Tension Control in Iridencleisis

It is generally accepted that iridencleisis lowers the intraocular tension, at least in part, by creating a fistula through which aqueous can drain to the subconjunctival bed. The fluid is then absorbed or, in the case of a thin cystic bleb, may pass transconjunctivally to mix with the tears. This mode of action of iridencleisis appears substantiated clinically by the fact that a good conjunctival bleb is usually associated with control of the intraocular tension, and, conversely, absence of the bleb is usually associated with lack of control.

Kronfeld and McGarry [16] have demonstrated that when external pressure is applied to an eye after iridencleisis, there is more rapid and more marked fall in the intraocular tension than when pressure is applied to a normal eye. This fall in pressure is accompanied by increase in size of the conjunctival bleb. They conclude that iridencleisis acts as a tension-normalizing operation by creating a new drainage channel for the intraocular fluid. Also in support of the mechanical action of iridencleisis is the report of Holth,[5] in which pigment-lined fistulous tracts were demonstrated in eyes in which iridencleisis had been performed.

The presence of a positive Seidel fluorescein test in eyes with a thin cystic bleb substantiates the transconjunctival passage of aqueous. By measuring the ascorbic acid content, Kronfeld [17] has demonstrated that the fluid appearing on the conjunctival surface of thin-walled, polycystic blebs is not derived from tears or other conjunctival secretions. He also has found that the rate of appearance of this fluid is increased by applying external pressure to the eye and concludes that this fluid is probably aqueous.

Rarely, the tension remains elevated in the presence of an apparently functioning bleb. However, in such instances, the bleb

has a thick covering of fibrous tissue which limits its effectiveness. In an occasional case, the tension is normalized after iridencleisis even where there is no clinical evidence of filtration. Reese [15] has stated that iridencleisis may control the intraocular tension in three ways: (1) by creating a filtering sluiceway; (2) by iridodialysis, in that the angle is freed over the area of the coloboma, and (3) by the pull of the iris pillars tending to tauten the iris and to prevent it from blocking the angle inferiorly. The latter two theories may explain why the tension is occasionally controlled after iridencleisis when there is no evidence of external filtration.

Operative Technique

The lashes are trimmed; routine benzalkonium (Zephiran), iodine, and alcohol skin preparation is employed, and silver proteinate is instilled in the eye, followed by copious irrigation with isotonic saline. Lid akinesia is obtained by injection of 2% lidocaine (Xylocaine) with 1:20,000 epinephrine, utilizing the O'Brien technique; anesthesia and akinesia of the extraocular muscles are obtained by retrobulbar injection of 2 cc. of 4% lidocaine with 1:20,000 epinephrine.

A Parke lid speculum is placed in position. The upper bulbar conjunctiva is slid forward, while a superior rectus fixation suture is inserted, permitting preparation of a large conjunctival flap. Approximately 0.33 cc. of 1:1,000 epinephrine is injected beneath the conjunctiva and anterior extension of Tenon's capsule. Pressure is applied over the epinephrine bleb with a cotton-tipped applicator until the solution undermines the entire area of the proposed flap. A conjunctival incision is then made along a line which normally lies about 10 mm. above the limbus; this incision is begun to one side of the superior rectus, penetrating down to bare sclera. One blade of a pair of Stevens scissors is inserted here, swept in front of the muscle insertion, and then backward before closing the blades; this gives a broad thick flap yet avoids damaging the muscle sheath. The completion of preparation of the flap can usually be accomplished by rolling the flap downward with a cotton-tipped applicator; rarely is further dissection necessary.

A transverse incision through the sclera, approximately 3.5 to 4 mm. in length, is begun 2.5 mm. posterior to the limbus with a Lundsgaard knife; this "scratch" incision is extended in a plane parallel to the iris, entering the chamber deep in the angle. The two ends of the incision are squared off with the knife so that the inner aspect of the incision is fully as long as its outer length. Before proceeding further, a dry field is obtained; this can usually be accomplished by application of epinephrine 1:1,000 solution. Rarely, it is necessary to use a minimal amount of diathermy coagulation.

The posterior lip of the scleral incision is depressed with resulting prolapse of the iris. The iris is grasped with smooth-tipped forceps and drawn outward and upward, with resulting tension being exerted on the iris insertion. Traction is continued until an iridodialysis is effected from approximately 11:30 to 12:30 o'clock. A radial iridotomy is then accomplished by inserting a scissors blade from the iridodialysis opening out through the pupillary opening (both of these being outside the eye at this stage), releasing the forceps, and then closing the scissors so as to cut the iris and allow it to drop without further manipulation. The conjunctival flap is smoothed upward over the iris pillars and closed with a running 000000 nonabsorbable (silk) surgical suture; the suture is not tied at either end. Atropine 1% is instilled, and the eye is covered with a sterile dressing and a metal protector. The other eye is also covered until the following morning.

General Considerations

1. *Dissection of the Conjunctival Flap.*—We believe it is desirable to have a thickly covered, diffusely filtrating bleb after iridencleisis. It is true that a thin, ectatic, well-circumscribed bleb will often give ex-

cellent control of tension; however, danger of hypotony or of late intraocular infection is always present. Friedenwald [18] has emphasized that very gentle dissection of the flap is of great importance and that hemorrhage into the area of the flap is usually accompanied by fibroblastic proliferation, which decreases the efficiency of the filtration bed. Chandler [19] also has emphasized that bleeding under the flap favors the development of scar tissue. We believe that injection of epinephrine solution subconjunctivally in the area of the proposed filtration bed is of value. In the first place, this reduces bleeding. Secondly, if the injection is given right next to sclera, beneath the subconjunctival fibrous tissue which extends anteriorly from Tenon's capsule, it causes separation in the proper plane of dissection.

2. *Scleral Incision.*—In the literature, one finds that one of three methods is usually employed for entry into the anterior chamber: use of a keratome, use of a cataract knife, or an *ab externo* approach with a Lundsgaard or some other knife appear to enjoy about equal popularity. We have some preference for the use of a Lundsgaard knife. The incision is begun rather posteriorly and continued in a plane parallel to the iris, entering the anterior chamber deep in the angle. We agree with Reese,[15] who has emphasized the importance of not making the incision too far into the cornea with a resulting shelf. Chandler [19] has observed that when the tongue of iris must go around a corneal shelf to reach the conjunctival tissue, a filtering scar is less apt to develop. Also of importance is the difficulty encountered in prolapsing the iris when the incision is placed too far anteriorly. Perhaps most important of all, however, is the fact that a posteriorly placed incision is more likely to yield a thick conjunctival covering for the bleb than an anterior one.

An incision of not more than 3.5 to 4 mm. in length is adequate, provided that the inner aspect of the incision is fully as long as its outer aspect, so that iris prolapse can be obtained without difficulty. There is no apparent advantage in wide separation of the iris pillars; in fact, an overly long incision probably results in an increased incidence of delayed reformation of the anterior chamber during the immediate postoperative period. It is our experience that with a relatively small incision the anterior chamber usually reforms by the time the conjunctival flap has been sutured.

3. *One- or Two-Pillar Iridencleisis.*—For some years there has been a rather lively discussion regarding the relative merits of one- or two-pillar iridencleisis. The two main arguments advanced in favor of the single-pillar procedure are that the updrawn pupil is avoided and that should cataract extraction be indicated at a later date, the extraction can be done temporally, thereby avoiding the filtering bleb. Both of these arguments are negated in our experience. If the iridencleisis incision has been made 2.5 mm. behind the limbus, there generally is plenty of room for a cataract incision anterior to the filtering bleb, and upward displacement of the pupil has not proved to be a problem. We incarcerate both pillars, feeling that this increases our chances of successful control of tension, particularly in view of the fact that one of the pillars might fail to create a permanent fistulous tract. Troutman [20] has analyzed the results obtained in 159 iridencleises. He found the glaucoma controlled in 72 of 105 one-pillar iridencleises (69%) and in 49 of 54 two-pillar iridencleises (90%). He believed these results constituted valid statistical evidence in favor of two-pillar iridencleises.

4. *Iris Manipulation.*—There seems to be general agreement that a minimum of handling of the iris is most essential in obtaining a successful result. Maintenance of an intact pigment epithelium is probably the most important single factor in successful iridencleisis. Fibrosis will not penetrate an intact layer of pigment epithelium; therefore, a permanent fistulous tract is maintained through which aqueous can reach the conjunctival bed. Sugar [21] states

that he has become increasingly impressed with the need for healthy iris pigment epithelium in obtaining a successful result with the iris-inclusion operation. He notes that when the pigment epithelium disperses at the time of operation, fewer filtering belbs are obtained than with intact pigment.

5. *Iridodialysis.*—A small iridodialysis superiorly is of at least theoretical value in two ways: 1. The angle is freed of obstruction of any remaining iris root in the area of the coloboma; 2. Tension exerted on the iris may break newly formed peripheral synechiae outside the area of the actual iridodialysis. Whether increased bleeding from iridodialysis negates or more than negates these theoretical advantages remains a moot question in our minds.

Report of Cases

During the period from Jan. 1, 1954, to June 30, 1957, iridencleisis was utilized at the Henry Ford Hospital in the surgical treatment of varied types of glaucoma in 95 eyes. The operation was performed bilaterally in 24 patients. Thirty-one men and forty women are included in the series. The iridencleises were performed by members of the permanent and resident staff. The average hospital stay was 9.5 days. All of the cases are included in enumerating the operative and immediate postoperative complications. However, in evaluation of results obtained, only those cases having a minimum of four months' follow-up are included. This requirement is met in the case of 86 eyes; in these, the follow-up period ranges from 4 to 45 months (average, 23 months).

Criteria for "Success".‡—A result is termed successful only if the following requirements are met:

1. The tension must be controlled within normal limits, with or without the use of miotics. With respect to the 1954 revised tonometric scale, the upper limit of "normal" is here considered to be 23 mm. Hg Sklar. No absolute value is taken as the lower limit of normal, the delimiting criterion in an eye with low tension being whether or not there is hypotony such as to impair visual function.

2. There must be no progressive loss of visual field after surgery.

3. There must be no permanent and disabling injury to the eye as a direct result of the surgical procedure.

Classified according to the above criteria, a successful result was obtained in 72 of the 86 cases followed for a minimum of four months (Table 1). Miotics were required in 18 of the 72 cases classified as having a successful result (Table 2). Failure was encountered in 14 cases (Table 3).

For the purpose of analyzing results obtained, the 86 cases with adequate follow-up have been classified into one of three categories: Acute congestive glaucoma, chronic open-angle glaucoma, and chronic narrow-angle glaucoma. Iridencleisis was not untilized in the treatment of aphakic glaucoma, secondary glaucoma, or congenital glaucoma during the period of this survey.

TABLE 1.—*Results in Eighty-Six Cases with Follow-Up Periods of Four to Forty-Five Months*

Type of Glaucoma	Success	Failure
Acute congestive	14	1
Chronic open-angle	22	5
Chronic narrow-angle	36	8
Totals	72	14

TABLE 2.—*Successes (Seventy-Two Cases)*

Type of Glaucoma	Controlled	
	Without Miotics	With Miotics
Acute congestive	11	3
Chronic open-angle	16	6
Chronic narrow-angle	27	9
Totals	54	18

‡ These criteria for "success" have been enumerated in a previous publication by us regarding evaluation of results obtained in cyclodialysis[2] and are purposely identical so that some comparison of the two operations can be made.

TABLE 3.—*Failures (Fourteen Cases)*

Type of Glaucoma	Elevated Tension		Tension Too Low	Field Loss Without Elevated Tension
	Without Field Loss	With Field Loss		
Acute congestive	0	1	0	0
Chronic open-angle	2	2	0	1
Chronic narrow-angle	3	3	1	1
Totals	5	6	1	2

Acute Congestive Glaucoma.—The 15 cases in this group exhibited the classical signs of pain, congestion, steamy cornea, markedly decreased vision, and marked elevation of intraocular pressure. In 12 instances, the tension was reduced appreciably prior to surgery by intensive use of miotics and acetazolamide (Diamox); in the remaining three cases, the tension remained markedly elevated up to the time of surgery. There were 14 successful results, including 11 eyes normalized without miotics and 3 eyes in which miotics were required. There was one failure in this group:

CASE 1.—In this eye the tension was 40 mm. Hg Sklar six weeks postoperatively. The bleb was described as completely fibrosed with no evidence of filtration, and there was progression of field loss. Some two months after iridencleisis, a corneoscleral trephine was done with satisfactory control of tension and no further progression of field loss.

Chronic Open-Angle Glaucoma.—Iridencleisis was done on 27 eyes classified as having chronic open-angle glaucoma. The 22 successful results include 16 eyes normalized without miotics and 6 eyes in which miotics were required. Five cases were classified as failures. The average age in this group was 62 years. The average tension preoperatively was 30 mm. Hg Sklar under medical therapy and relatively nonlabile. Aqueous outflow studies were performed prior to surgery in 21 cases: The outflow coefficient was below 0.13 in 16 cases and above 0.13 in 5 cases. Visual field changes prior to surgery were as follows: Normal, 5; minimal loss, 6; moderate loss, 11, and severe loss, 5. The cases in which failure was encountered are described briefly as follows:

CASE 2.—In a 76-year-old white woman, the tension rose to 35 mm. Hg Sklar 10 days postoperatively. No filtering bleb was present at that time. The tension remained elevated, and three months after iridencleisis a cyclodialysis was performed. The tension was controlled during the hospital stay; no further follow-up is available.

CASE 3.—A 40-year-old white man had a shallow anterior chamber begining on the first postoperative day; the chamber was described as flat from the 6th to the 11th days. On the 11th postoperative day, an air injection was done with resulting reformation of the anterior chamber. Three months after surgery the tension was 37 mm. Hg Sklar. Cyclodialysis was performed with subsequent control of tension.

CASE 4.—A 65-year-old white man had a moderate hyphemia present on the first postoperative day; as the hyphemia cleared, presence of a vitreous hemorrhage was noted. On the third postoperative day the tension was 39 mm. Hg Sklar. The tension then ranged from 31 to 51 mm. Hg Sklar during the next three weeks. Absorption of the blood in the vitreous was accompanied by slowly progressive cataractous changes. During the past two years, the tension has varied from 16 to 31 mm. Hg Sklar while on miotics. Visual field loss has shown some apparent progression, although progression of lens opacities renders this uncertain, since these affect comparison of similar isopters.

CASE 5.—In an 80-year-old white man the tension postoperatively has ranged from 15 to 30 mm. Hg Sklar, averaging 26 mm. Miotics were prescribed but used sporadically by the patient. Visual field loss was moderate prior to surgery. One year postoperatively there is severe loss of field with only a temporal island of vision remaining.

CASE 6.—A 65-year-old white man exhibited advanced glaucoma with marked

cupping of the disc and severe field loss prior to surgery. The tension has been controlled on eserine 0.25% twice daily during the three-year postoperative period. However, there has been further progression of field loss with only 3 to 4 degrees of central field remaining.

Chronic Narrow-Angle Glaucoma.—Iridencleisis was performed on 44 eyes having chronic narrow-angle glaucoma. The 36 successful results include 27 eyes normalized without miotics and 9 eyes in which miotics were required. Eight cases were classified as failures. The average age in this group was 60 years, and the average intraocular tension while on the miotics prior to surgery was 29 mm. Hg Sklar. The intraocular tensions while on miotics were more labile and exhibited a wider range of variation than the tensions recorded in the chronic simple glaucomas. Aqueous outflow studies were done in 27 cases: The outflow coefficient was below 0.13 in 19 cases and above 0.13 in 8 cases. Visual field changes were recorded as follows: Normal, 11; minimal loss, 15; moderate loss, 11; severe loss, 4, not recorded, 3. The eight eyes classified as failures are described briefly as follows:

CASE 7.—In a 65-year-old Negro man three months after iridencleisis, the tension was 29 mm. Hg Sklar with no evidence of a filtering bleb. Progression of visual field loss had occurred. A cyclodialysis was done three months after iridencleisis with subsequent control of tension and no further field loss.

CASE 8.—In a 61-year-old white woman three months after iridencleisis, the conjunctival bleb appeared scarred down without any evident filtration. The intraocular tension was elevated to 33 mm. Hg Sklar. Some progression of visual field loss was noted. A cyclodialysis was performed 17 months after iridencleisis with control of the intraocular tension and no further field loss.

CASE 9.—In a 64-year-old white man, the glaucoma initially was well controlled after iridencleisis. However, there was rapid progression of cataractous changes, and a cataract extraction was done two months after iridencleisis. Since cataract extraction, there has been no evidence of a filtering bleb; six months postoperatively the tension has risen to 28 mm. Hg Sklar.

CASE 10.—A 63-year-old white woman exhibited severe constriction of visual fields prior to surgery. On the first postoperative day the eye operated on was firm to fingers, and it was found that one of the iris pillars had prolapsed back into the anterior chamber. The patient was reoperated on, and the iris pillar replaced in the scleral incision. Sixteen months postoperatively the tension had risen to 32 mm. Hg Sklar without miotics. The patient was placed on 4% pilocarpine four times daily with only fair control of the intraocular tension.

CASE 11.—In a 62-year-old white woman the tension ranged from 35 to 40 mm. Hg Sklar two months postoperatively. Only fair control of the intraocular tension was obtained with miotics. A cataract extraction was done on this eye approximately two and one-half years after iridencleisis. After cataract extraction the tension has remained well within normal limits. However, the patient exhibits increased visual field loss as compared with her visual fields prior to iridencleisis.

CASE 12.—A 60-year-old white woman has had persistent hypotony for 22 months after iridencleisis. The tension has ranged from 5 to 10 mm. Hg Sklar. During the first few postoperative months, macular edema was present; as this subsided, macular degenerative changes became apparent.

CASE 13.—A 50-year-old white man exhibited moderate constriction of the visual fields prior to surgery. After iridencleisis the tension has been well controlled on miotics. Nevertheless, there was steady progression of visual field loss, and 39 months postoperatively vision is limited to light perception.

CASE 14.—A 58-year-old white woman had an uneventful postoperative recovery after iridencleisis, and the tension was well

controlled initially without miotics. However, four months after surgery the eye developed acute glaucoma with tension elevated to 53 mm. Hg Sklar. The anterior chamber had become completely flat, with apparent anterior dislocation of the lens. After cataract extraction, the chamber remained very shallow. Seventeen days after cataract extraction injection of air into the anterior chamber was performed. Four days later air injection and discission of the anterior hyaloid face was done. The tension was not controlled. Cyclodialysis was performed, the cleft closed immediately, and a few days later another cyclodialysis was done. After the second cyclodialysis the tension has remained within normal limits. However, there was extensive hemorrhage into the vitreous after the second cyclodialysis. Six months later there has been some absorption of the vitreous hemorrhage, but vision is still limited to light projection.

Early Complications

During the immediate postoperative peroid, the most frequently encountered complications (Table 4) were (1) hyphemia and (2) failure of reformation or failure to maintain an adequate anterior chamber. Vitreous hemorrhage was noted in one instance, and one of the pillars slipped back into the anterior chamber in one case.

TABLE 4.—*Early Complications (Ninety-Five Operations)*

	%
Hyphemia	30
Shallow or flat anterior chamber	26
Vitreous hemorrhage	1
Retraction of iris pillar	1

1. *Hyphemia.—Immediate hyphemia* was present upon completion of surgery in nine cases and was described as minimal in six and moderate in two cases; in one case the hemorrhage was described as brisk, filling the entire anterior chamber. These immediate hyphemias usually seem to come from bleeding at the iris insertion along the area of the iridodialysis. *Delayed hyphemia* occurred in 20 eyes, usually occurring on the first, second, or third postoperative days. In two instances there was slight recurrence of hyphemia, one on the fifth and one on the seventh postoperative days.

In summary, hyphemia, either immediate or delayed, occurred in 29 of the 95 eyes (30%). The hyphemia was minimal in most cases, and in all instances had cleared prior to discharge from the hospital. In the cases with adequate follow-up, the tension was controlled in 21 of 27 eyes (78%) in which hyphemia occurred and in 54 of 59 cases (92%) in which no hyphemia was noted. These figures, although suggestive, do not offer valid statistical evidence that hyphemia plays a role in failure to control tension. However, at least from a theoretical viewpoint, we believe hyphemia is detrimental in that it may cause increased scarring along the fistulous tract and in the conjunctival bed.

2. *Shallow or Flat Anterior Chamber.*—(*a*) In 17 cases the anterior chamber was described as *very shallow but not flat* for varying periods during the first two weeks postoperatively. In five of these eyes the shallow chamber was noted on the first postoperative day; in the remaining 12 eyes the chamber usually became shallow three to four days after surgery. In all 17 eyes the chamber deepened satisfactorily without operative intervention, usually within two to three days.

(*b*) In eight additional eyes the chamber was described as being *completely flat* at some time during the postoperative period. In four of these eyes the anterior chamber deepened spontaneously, and the tension has remained within normal limits. In the other four eyes injection of air into the anterior chamber was necessary, and in one of these, air injection had to be repeated five days after the initial injection. In two of the cases requiring air injection, the tension was subsequently controlled without miotics. In one case the tension was not controlled, and cyclodialysis was done four months

later with subsequent control of tension. No follow-up was obtained in the fourth case.

In summary, shallow or flat anterior chamber was noted in 25 eyes. Considering only the eyes where there was adequate follow-up, the tension was controlled in 21 of 23 eyes (91%) in which the chamber was shallow or absent and in 54 of 63 eyes (86%) in which the anterior chamber remained adequately formed. In this series it would seem that shallow or flat anterior chambers had little or no effect upon the eventual result obtained.

Late Complications

Late complications encountered after iridencleisis in this series (Table 5) include failure to control tension, progression of visual field loss, cataract formation, hypotony, and upward displacement of the pupils. Intraocular infection and sympathetic ophthalmia did not occur.

TABLE 5.—*Late Complications (Eighty-Six Operations)*

	%
Tension elevated	13
Progression of field loss	9
Cataract	36
Hypotony	1
Upward displacement of pupil	2

1. *Elevation of Intraocular Tension* (Eleven eyes).—Failure was usually evident within six weeks after surgery and in most cases was accompanied by marked scarring and fibrosis in the area of the conjunctival bed with resulting decreased or absent evidence of filtration. However, in two of these cases large filtering blebs were described as being present even at the time of elevated intraocular tension (35 to 40 mm. Hg Sklar two to three months after iridencleisis in each instance). Sugar[21] has described similar experiences and states that the return of elevated intraocular tension in the presence of a well-cushioned bleb suggests the possibility of hypersecretion of aqueous. To our minds, progressive fibrosis within the bleb seems a more likely cause.

2. *Progression of Visual Field Loss* (Eight eyes).—Six of these eyes also exhibited continued elevation of the intraocular tension after surgery. In two eyes the visual field loss exhibited marked progression even though the intraocular tension was apparently well controlled.

3. *Cataracts.*—(*a*) There was *progression of preexisting lenticular opacities* in 10 eyes. In three of these eyes the progression was rapid, with marked reduction of vision within three to six months after surgery. The remainder progressed more slowly, with minimal to moderate decrease in acuity one to three years after iridencleisis.

(*b*) There was *cataract formation in previously clear lenses* in 21 eyes. The opacities usually appeared during the second or third postoperative years, the changes noted being "minimal" in 14 eyes and "moderate" in five eyes. In the remaining two eyes there was rapid development of marked cataractous changes during the early postoperative period.

4. *Hypotony.*—Hypotony sufficient to cause macular edema and subsequent macular degeneration occurred in only one eye. It is our impression that hypotony, and especially borderline hypotony, occurs much less frequently after iridencleisis than after cyclodialysis.

5. *Upward Displacement of the Pupil.*—Upward displacement of the pupil sufficient to impair vision occurred in only two eyes (of the same patient), and the decrease in visual acuity was slight.

Comparison of Iridencleisis and Cyclodialysis

In a previous report[22] we have summarized results obtained from cyclodialysis performed during the period from January, 1954, to July, 1956 (the iridencleisis series includes an additional year, extending up to July, 1957). Although the period of survey is similar, we realize that a completely valid comparison cannot be made because the number of cases is not

sufficiently large and, of more importance, the selection of cases was not made in a random manner for each operation. However, we believe that a comparison of some validity can be considered in those cases classified as having primary noncongestive glaucoma. In these cases we have had some preference in the past for cyclodialysis in chronic open-angle glaucoma and iridencleisis in chronic narrow-angle glaucoma (Table 6). It would appear that these

TABLE 6.—*Primary Chronic Glaucoma: Comparison of Results from Cyclodialysis and from Iridencleisis*

	Cyclodialysis		Iridencleisis	
Type of Glaucoma	Total No. Cases	No. Failures	Total No. Cases	No. Failures
Chronic open angle	52	5	27	5
Chronic narrow-angle	6	0	44	8
	58	5(9%)	71	13(18%)

preferences are not necessarily well founded in view of the results obtained. The proportions of success obtained in these two series is of the same magnitude (both for narrow- and for open-angle types) and would indicate that the two operations are of comparable effectiveness for primary noncongestive glaucoma.

It has been our opinion that iridencleisis is the operation of choice in cases of acute congestive glaucoma in which the acute attack has persisted long enough or has recurred often enough to cause permanent embarrassment of the outflow mechanism. In those cases of acute congestive glaucoma in which the tension is low between attacks, the response to miotics is prompt and the aqueous outflow coefficient is high, we can assume that there has been no formation of anterior peripheral synechiae to the extent to embarrass the aqueous outflow; in these cases we prefer to do a peripheral iridectomy.

We feel that cyclodialysis is the operation of choice in aphakic glaucoma which would account for the fact that there are no cases of this type included in the iridencleisis series. It is generally accepted that there is increased fibrosis and scarring in the area of the bleb after iridencleisis in members of the Negro race. For this reason, we have employed iridencleisis infrequently in Negroes and prefer to utilize cyclodialysis as the original surgical procedure.

Summary

The operative technique employed, the results obtained, and the complications encountered in 95 consecutive iridencleisis over a three-and-one-half-year period are presented. A successful result was obtained in 84% of the cases (acute congestive, chronic open-angle, and chronic narrow-angle glaucoma).

We believe iridencleisis is the operation of choice in those cases of acute congestive glaucoma in which permanent embarrassment of the outflow mechanism has occurred. It would appear that iridencleisis and cyclodialysis are of comparable effectiveness for chronic primary noncongestive glaucoma of either the open- or narrow-angle type (with the exception of those cases occurring in the Negro race, in which we would prefer cyclodialysis). We do not feel that iridencleisis is indicated in aphakic or other secondary glaucomas.

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Immunoelectrophoresis of Cataractous Lenses

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The history of immunology of lens proteins goes back to Uhlenhuth,[1] who 55 years ago showed by precipitation tests the organ specificity of some of the lens components. This was verified later by Burky, Woods, and Woodhall.[2] They found that mainly the so-called α-crystallin was organ-specific. Recently fractionation of lens proteins was improved by François, Rabaey, Wieme, and Kaminski.[3,4] Using Cohn's technique with alcohol precipitation in the cold[3] and paper, as well as agar gel electrophoresis,[4] they were able to produce as many as eight different fractions. Rao[5] used agar precipitin tests and found six components in bovine lens with rabbit antisera. Halbert and co-workers,[6,7] by means of gel diffusion technique, found up to five different lens antigens with homologous rabbit antilens sera. Further experiments were performed with several heterologous lens antisera in rabbits. The cross reactions among vertebrate lenses were found to be due to antigenic similarity of up to six of the components detected.

Clinical research on lens-induced eye diseases goes back to the paper of Straub,[8] who was the first to describe phacotoxic uveitis. Later Woods,[9] H. Müller,[10] and S. R. Irvine[11] did extensive studies on lens-induced uveitis. Experimental work along this line has been done by Burky,[12] François,[13] H. Müller,[10] and Lyda and Lippincott.[14] These experiments revealed that allergic reactions can be produced with homologous lens material using Staphylococcus toxin as adjuvant, and that immunization against homologous lens proteins can be done with Freund's[15] adjuvant.

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From the University Eye Clinic, Director: Prof. H. Goldmann.

Stimulus for the present studies was prompted by the observation of three cases of lens-induced uveitis. In these cases we were able to demonstrate aqueous humor antibodies against their own lens by the hemagglutination technique.[16]

The method of immunoelectrophoresis used in our experiments has been introduced by François and coworkers[4] for the study of lens proteins.

Method

The immunization of the rabbits for the production of antisera was done by the following procedure: Four rabbits received subcutaneous injections of a mixture of cataract lens homogenate with Freund's adjuvant once weekly during the first three weeks. This was followed by intraperitoneal injections of lens homogenate in saline alone once weekly for two more months. Two rabbits were immunized with ox-lens homogenate by the same procedure. Two other rabbits were given weekly intravenous injections only for two months. Blood samples were collected by puncture of the ear artery. The anticataract serum (ACS) and the anti-ox-lens serum (AOS) were lyophilized and stored at 4 C.

Cataract lenses were homogenized in 1 cc. of buffered isotonic saline and then centrifuged for 10 minutes at 3,000 rpm. The supernate solution, containing approximately 0.5% to 2.0% soluble proteins, was recovered, and a small drop of 0.01 cc. was placed on the surface of an agar slide with a capillary pipette. The slide was then placed under a continuous current of 40 V and 75 amp for 60 minutes in an ice-cold electrophoresis chamber filled with barbiturate buffer (pH 8.6 and 0.1 ionic strength). After electrophoresis two small grooves were cut out of the agar parallel

to the edge of the slide. These grooves were then filled completely with antiserum. The slides were left in a moist chamber in the icebox for four days, then washed with saline for 12 hours, and dried with a filter paper. By this procedure, all soluble components are removed and only the precipitates remain on the slide. They were stained with amidoblack, and the excess was removed by washing with methanol (details of method described by J. J. Scheidegger [17]).

Results

The pattern obtained by agar electrophoresis alone with a cataract lens is shown in Figure 1. This lens from a 45-year-old man revealed three fractions by measuring

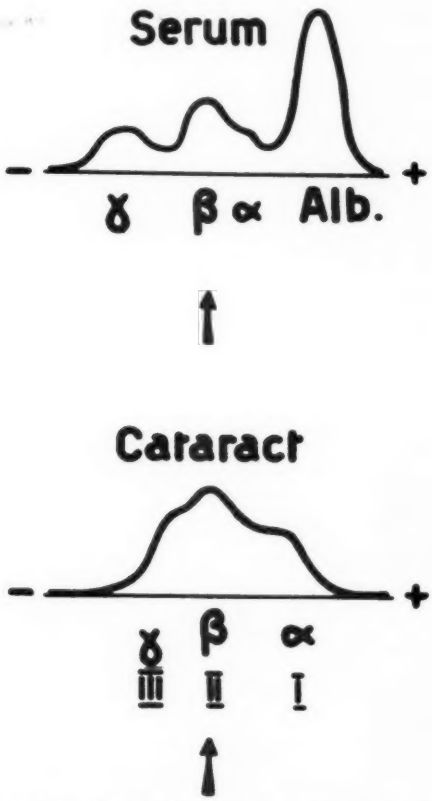

Fig. 1.—Electropherogram of normal human serum and of human cataract lens on agar slide. Arrow indicates point of departure.

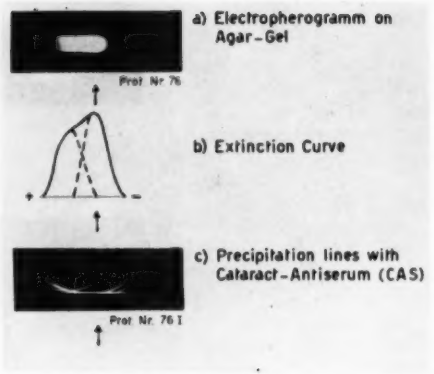
a) Electropherogramm on Agar-Gel
Prot. Nr. 76
b) Extinction Curve
c) Precipitation lines with Cataract-Antiserum (CAS)
Prot. Nr. 76 I

Fig. 2.—(*a*) Electropherogram of human cataract lens on agar slide. (*b*) Extinction curve after densitometry. (*c*) Precipitation lines appearing upon diffusion of anticataract serum of rabbit (ACS).

the extinction of the stained slide with a photoelectric cell. These fractions are usually called α-, β-, and γ-crystallin, or Fraction I, II, and III. The α-crystallin is the fastest protein, the β-crystallin moves very little under the condition of our experiment, and the third fraction, the γ-crystallin, migrates towards the cathode. The clear lens of a 20-year-old patient in Figure 2 shows only two distinct fractions. But if one now lets this lens react with the anticataract serum (ACS), one gets three definite lines. François and coworkers [4] have called these lines *A* and *A'* for the γ-crystallin, *B* and *B'* for the β-crystallin, and *C* and *C'* for the first or α-crystallin. This designation was chosen according to the time of appearance of the precipitation lines, the *A*-lines appearing first and the *C*-lines latest. It seems to me more logical to call *A* and *A'* the lines corresponding to the α-crystallin and *C* and *C'* the lines corresponding to the γ-crystallin, and I have therefore chosen this designation in the slides.

Experiments with ACS Alone.—Of the 50 senile cataracts which were run in this assay, the results appear to fall into two groups. The major portion of the lenses (31 cases) show five precipitation lines. Although the single lines become often very long and join together in the middle they

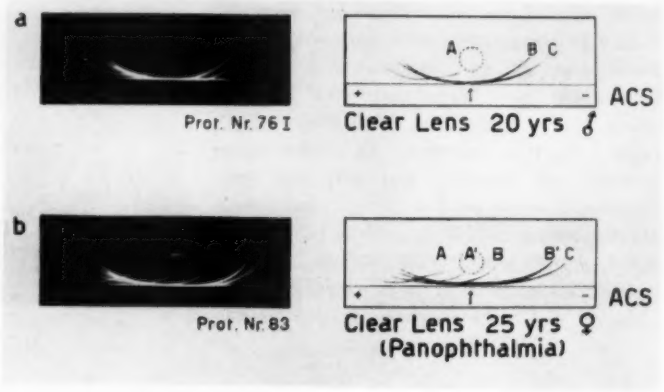

Fig. 3. — Immunoelectropherogram of (*a*) normal human lens showing three (*A*, *B*, *C*) and (*b*) clear human lens in a case of panophthalmia showing five (*A*, *A'*, *B*, *B'*, and *C*) precipitation lines with ACS, corresponding to the α-crystallin (*A* and *A'*), to the β-crystallin (*B* and *B'*) and to the γ-crystallin (*C*). Arrow and dotted circle indicating point of departure.

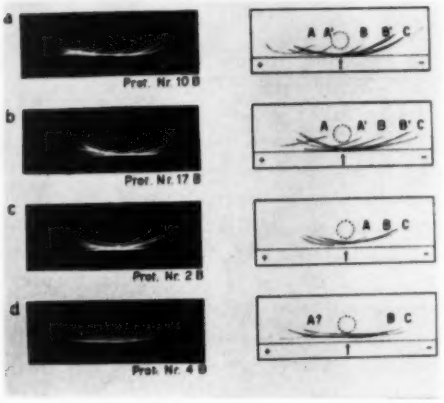

Fig. 4.—Immunoelectropherogram of human cataract lenses; (*a*) and (*b*) immature cataracts with five precipitation lines, (*c*) and (*d*) mature cataracts with three and two precipitation lines, respectively, with ACS.

Immunoelectrophoresis of Different Cataracts with Anticataract Serum and Anti-Ox-Lens Serum

	No. Cases Examined
Cataracta congenita	6
Cataracta traumatica	14
Cataracta juvenilis	2
Cataracta myotonica	1
Cataracta diabetica	1
Cataracta complicata with heterochromia	2
Cataracta complicata	5
Cataracta praesenilis	5
Cataracta senilis matura	2
Cataracta senilis hypermatura	4
Clear lens	3
Rabbit lens	1
Ox lens	1
Dog lens	1

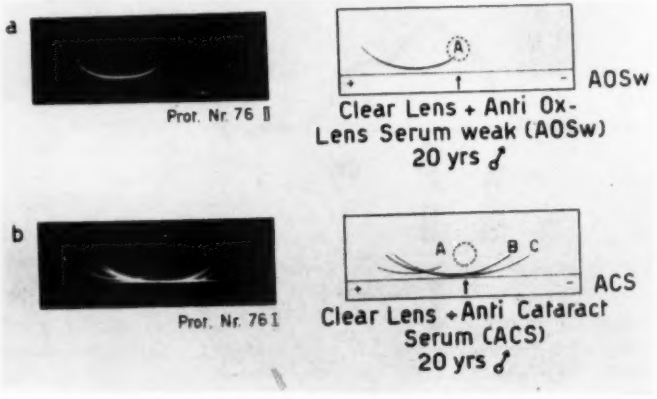

Fig. 5. — (*a*) Immunoelectropherogram of a clear human lens with anti-ox-lens serum of rabbit with low antibody content (AOSw) showing a single precipitation line (*A*) corresponding to the α-crystallin. (*b*) The same human lens after reaction with ACS reveals three precipitation lines (*A*, *B*, and *C*).

all separate very distinctly at the end (Fig. 4*a* and *b*). This separation is certainly not an artifact, since it is seen in all these cases of senile cataract. A smaller group of 19 cataract lenses has slightly different aspect. In this group we do not see the separation of precipitation lines as clearly as in the first group (Fig. 4*c* and *d*). Clinically the first group with five fractions is made up of lenses with immature cataract. The second group contains all mature cataracts, where the lens is totally opaque.

Experiments with ACS and AOS.—In this second series I attempted to determine whether the five fractions demonstrated in the first experiment with senile cataracts were species-specific or not. For this purpose 50 cataract lenses were collected from patients of various ages (Table). In Figure 5*a* we see the reaction between a normal human lens and an anti-ox-lens serum with low antibody content (AOSw). Only the *A*-line appears in this slide, which corresponds to the *α*-crystallin. But the same lens treated with a very potent AOS reveals that the same five fractions *A*, *A'*, *B*, *B'*, and *C* are present (Fig. 6*a*).

Next the reaction of AOS and ACS together with the normal human lens was studied. It can be seen (Fig. 6*b*) that the precipitation lines appear in an almost absolutely symmetrical pattern. In some cases

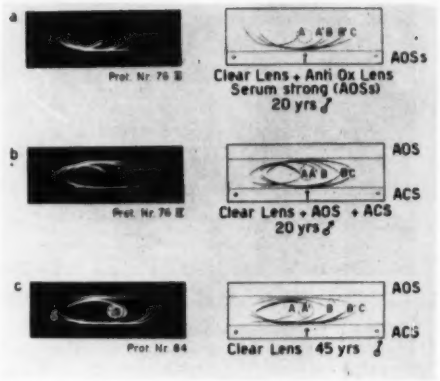

Fig. 6.—(*a*) A clear human lens reacting with a potent anti-ox-lens serum (AOSs) shows five precipitation lines (*A*, *A'*, *B*, *B'*, and *C*). (*b*) After double diffusion of ACS from below and AOS from above, a reaction of identity appears between the two *A*-lines and the two *B'*-lines. Five precipitation lines appear on the side of the AOS and only three precipitation lines on the side of the ACS. (*c*) A similar picture is produced with a clear human lens of a 45-year-old patient. But here three lines only appear on the side of the AOS and five lines on the side of the ACS.

the precipitation lines join in the middle of the slide to form a very fine curving line, which can only be seen on the original slide and does not lend itself for photography. This indicates that the two precipitation lines are immunologically identical. Figure 6*c* demonstrates similar findings in another clear human lens of an eye removed for a tumor of the maxillary bone.

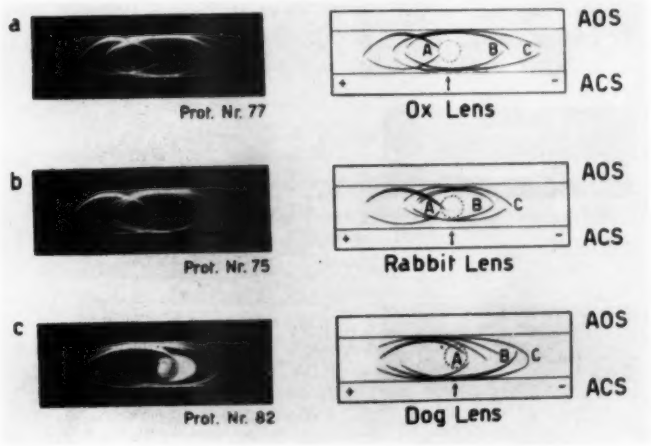

Fig. 7.—(*a*) Double-diffusion immunoelectropherogram of ox lens showing three symmetrical precipitation lines with ACS and AOS. Similar pictures are produced with (*b*) rabbit lens and (*c*) dog lens.

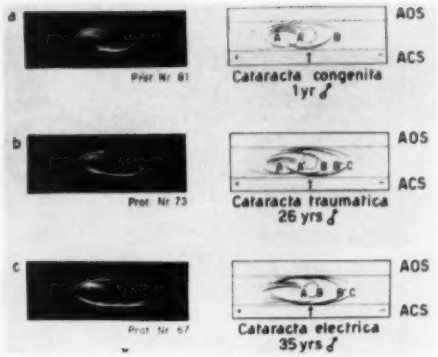

Fig. 8.—Immunoelectropherogram with ACS and AOS: (*a*) a congenital cataract shows three precipitation lines with ACS and a very broad *A*-line with AOS; (*b*) a traumatic cataract of a young adult shows five precipitation lines with ACS but only three with AOS. No symmetrical line is found for the *A*-line with ACS. (*c*) A cataract after electrical injury shows four precipitation lines with ACS and AOS.

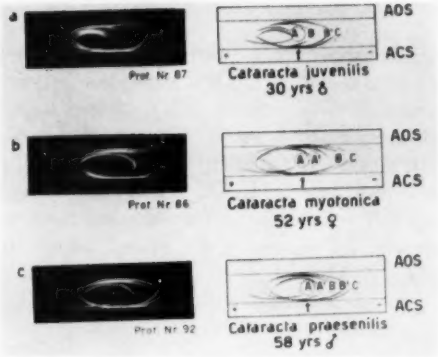

Fig. 9.—Immunoelectropherogram with ACS and AOS (*a*) from a juvenile cataract, (*b*) from a myotonic cataract, and (*c*) from a presenile cataract, showing all four precipitation lines with ACS and AOS. (*b*) and (*c*) have asymmetric *A*-lines with ACS.

There is a single fast-moving and faint precipitation line, which is only produced by the ACS. Figure 7 shows that ox lens, rabbit lens, and dog lens all react with ACS similarly. They all have at least three identical antigens.

The following figures deal with cataract lenses of different etiology and age.

The congenital cataract shows very distinct lens fractions. Most cases have at least three different lines. Very similar immunoelectropherograms are produced with traumatic cataracts of young adults. Lens opacity after electrical injury does not differ from traumatic cataracts of the same age group (Fig. 8*a*, *b*, and *c*).

Juvenile myopic cataract, myotonic cataract, and presenile cataract have four

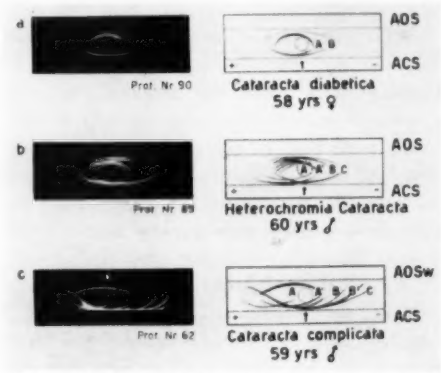

Fig. 10.—Immunoelectropherogram with ACS and AOS: (*a*) a mature diabetic cataract shows a single *A*-line with ACS and two lines with AOS, (*b*) a case of heterochromia shows three precipitation lines with ACS and AOS, and (*c*) a complicated cataract shows six precipitation lines with ACS only.

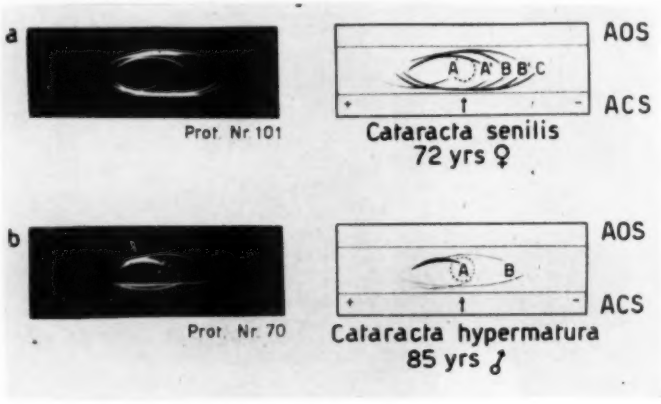

Fig. 11. — Immunoelectropherogram with ACS and AOS: (*a*) senile cataract with five precipitation lines with ACS and an asymmetric *A*-line, and (*b*) senile hypermature cataract with two precipitation lines with ACS and AOS.

precipitation lines (Fig. 9*a*, *b*, and *c*). A diabetic cataract has only a single *B*-line with ACS, while a case of heterochromia has very broad *A*-lines with AOS, and a case of a cataracta complicata even shows six lines with ACS (Fig. 10*a*, *b*, and *c*).

Simple senile cataracts have four-five lines with ACS and AOS. Hypermature cataracts do not differ from mature cataracts (Fig. 11*a* and *b*), in that there are no new proteins detectable but rather less than in mature cataracts.

Comment

These results of immunoelectrophoresis of lens protein represent a fairly good estimation of the different antigenic components of human lens.

A totally mature cataract shows a maximum of three precipitation lines, whereas the immature cataract shows at least three and very often five precipitation lines. This is possibly due to a difference in the concentration of soluble proteins. The three lines of mature cataract do not differ immunoelectrophoretically from those present in immature cataract.

The most interesting finding was that both AOS and ACS produced very similar precipitation lines provided one uses a potent AOS. If one uses a weak AOS, then only one precipitation line will appear, belonging to the α-crystallin. This could be misinterpreted to indicate that only α-crystallin is organ-specific. From these studies it appears that the α-, β-, and γ-crystallin of ox lens, rabbit lens, dog lens, and human lens are immunochemically similar. Therefore not only α- but β-, and γ-crystallin also are organ-specific. These findings are in agreement with previous observations with homologous anti-rabbit-lens antisera which revealed that as many as six components might be involved in organ-specificity (Halbert and co-workers[6,7]). The only evidence of species-specificity is the faint, fast-moving fraction which forms a precipitation line with ACS and not with AOS. This is purely speculative and will be studied further.

It seems that cataracts of younger age groups have typical immunoelectrophoretical pattern, but the present series are still too small to draw any definite conclusions. We can say that congenital and traumatic cataracts in children present the same behavior in that the different fractions are more easily separated. But the precipitation lines are similar in number and appearance to those of adult lenses. One diabetic cataract was available for this study and showed only a single *B*-line, while other cataracts of the same age group show at least four lines. Perhaps this is due to the fact that the diabetic cataract was quite mature. One case of complicated cataract had six precipitation-lines; a very faint new line appears between *A* and *B* line.

The immunoelectrophoretic method of study deals only with the soluble protein fractions of the lens. The insoluble and denaturated proteins of the cataractous lens are not detected in this study. If, therefore, lens-induced uveitis is a toxic reaction to denaturated protein rather than an immunological one, this method would not be suitable.

The method of immunoelectrophoresis concerns only qualitative estimation of lens proteins. Quantitative conclusions should not be drawn from these pictures. Furthermore, the relation between quantity of antigen and antibody is of extreme importance in all precipitation reactions. We have seen that we could have been mislead by a weak AOS, which produced only one line, whereas a potent serum produced five lines. On the other hand, the quantity of antigen available is also of importance. I have been working so far with very small quantities (0.01 cc. of a 0.5%-2.0% protein solution), and it is conceivable that with greater quantities in higher concentration I could produce precipitation lines which did not appear with the micromethod.

Summary

An attempt was made to study lens-induced uveitis by means of immunoelectrophoresis. Antisera were produced in

rabbits against cataract proteins (ACS) and against ox-lens proteins (AOS). Electrophoresis of cataracts was performed in agar gel, and precipitation lines appeared upon diffusion of antisera. Immature cataracts show a minimum of three and a maximum of five lines, whereas mature cataracts show a maximum of three lines. Cataracts of different age groups and different etiology have the same precipitation lines. The method of immunoelectrophoresis has, therefore, given no clues yet as to the etiology of lens-induced uveitis. Double-diffusion technique with ACS and AOS reveals that not only α-crystallin is organ-specific but β-, and γ-crystallin also.

Universitäts-Augenklinik.

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Recurrent Intraocular Hemorrhage in Young Adults (Eales' Disease)

Treatment with Continuous Subconjunctival Therapy with Hydrocortisone

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In 1954, I [1] reported my observations on 31 cases of recurrent intraocular hemorrhage in young adults, an entity commonly known by the name of Eales' disease but probably more correctly called retinal periphlebitis. The typical case usually occurs in an apparently healthy young man, with a sudden painless blurring of vision on awakening in the morning. The hemorrhages are characteristically in the periphery of the retina and are associated with the retinal veins, which show marked perivascular exudation, varying from a narrow path of sheathing to extensive exudation. As a rule, the veins tend to be dilated, but in some cases they may be beaded or varicose over short segments of their course. The hemorrhages are usually confined to the retina at the beginning, but it is only a matter of time until one occurs which is of sufficient magnitude to burst through the internal limiting membrane into the vitreous. Recurrence is a rule, and the vitreous usually never completely clears before another hemorrhage occurs; thus, the visual acuity at any given time is a poor measure of the ocular disability. The hemorrhages tend to become less frequent as time goes on and may cease altogether. The vitreous opacities may absorb, and normal vision may be recovered. The common complications are permanent vitreous opacities, vascularization of the vitreous, retinitis proliferans, chronic uveitis, and secondary glaucoma.

The clinical history and findings were so similar in all the cases that I concluded that the disease should be considered a clinical entity and not a manifestation of many diseased conditions.[2] Furthermore, it was postulated that the hemorrhages and exudation resulted from a hypersensitivity reaction in the walls of the peripheral retinal veins in persons who have been sensitized to the tuberculoprotein. Eight of the patients had active or healed pulmonary tuberculosis, and the skin tuberculin test was positive in 30 of the 31 patients. Three eyes were available for pathologic study, which revealed that some of the retinal vessels were surrounded by a few lymphocytes, but on the whole there was little if any inflammatory reaction in the retina around the vessels. The pathologic findings were compatible with the hypothesis that the disease has an allergic basis.

We are indebted to Arnold R. Rich [3] and his associates, who have demonstrated over the past 25 years that hypersensitivity can produce serious disturbances of the respiratory and alimentary tracts and of the cardiovascular, urinary, hematopoietic, and nervous systems and that it damages the connective tissues and is responsible for multiplicity of cutaneous disorders. The role played by tuberculin type hypersensitivity in chronic infection is an important one, for it can enormously intensify tissue damage and destruction. It is well known that the local inflammatory response to the tuberculoprotein antigen in this type of hypersensitivity is delayed and prolonged.

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The prevention of the hypersensitivity reaction by densitization may spare the body from unnecessary damage. Desensitization with old tuberculin is now rarely attempted because of the risk of general and focal reactions. Serious focal reactions occurred in two of the patients recorded by me [1] in 1954.

If the retinal periphlebitis (Eales' disease) is due to a hypersensitivity to tuberculoprotein, then the corticosteroids may reduce the allergic reaction as long as therapy is continued. It has been experimentally demonstrated that the beneficial effects of steroid therapy are due to an ability to block the tissue reaction to hypersensitivity.

Since my previous report on 31 cases of Eales' disease, an additional 24 cases have been under observation, making a total of 55 cases. In the past five years, 13 of the patients in the series of 55 cases have been under continuous therapy with subconjunctival injections of cortisone or hydrocortisone acetate, 1 cc. being injected subconjunctivally every two or three months. The patients selected for the treatment were those in whom the disease showed some signs of activity, namely, those in whom retinal hemorrhages could be observed ophthalmoscopically in the periphery of the retina. As long as hemorrhages in the retina were noted the disease was considered to be active, but when hemorrhages did not occur the condition was considered to be inactive.

The period of injections in this series of 13 patients receiving this form of continuous subconjunctival hydrocortisone therapy ranged from one to four years. As many as 18 subconjunctival injections have been made in a single eye over a four-year period without ill effect. Hydrocortisone acetate suspension in saline (intra-articular type) was used, 1 cc. containing 25 mg. It was observed that this amount of hydrocortisone usually required two or three months to become absorbed from beneath the conjunctiva, but in some cases the residue would be gone within five or six weeks, while in other cases the residue did not absorb for three or four months or longer.

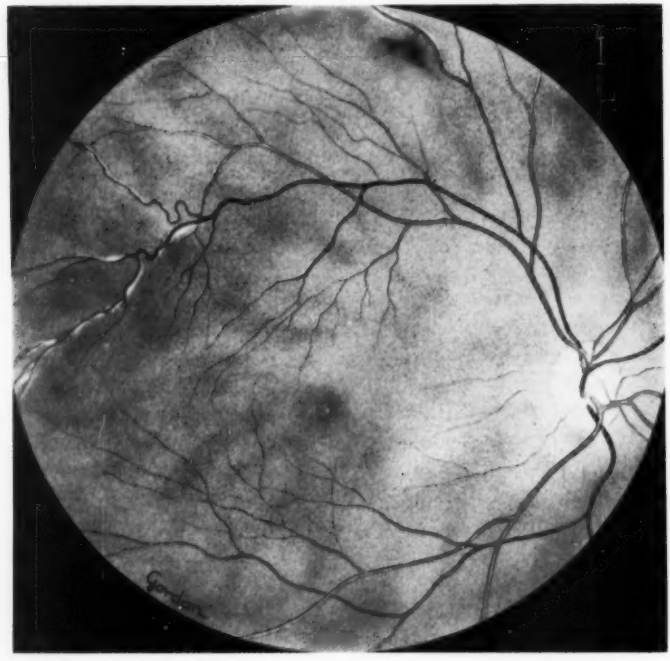


Fig. 1.—Eales' disease, November, 1953, showing intraretinal hemorrhage and perivascular sheathing.

Fig. 2.—Same eye, March, 1958, showing whorls of newly formed venules.

Of the 13 cases comprising this series under treatment, 10 have had no complication or further signs of progression of the disease, in that no new hemorrhages were noted in the retina. However, a spontaneous vitreous hemorrhage occurred in one patient six weeks after an injection of 1 cc. of hydrocortisone (Case 14 in my previous report [1]).

Figure 1 shows the right eye of a man, now aged 41, who has been under observation for 15 years. The drawing was made in November, 1953 (Case 15 in my previous report [1]), and it shows a small absorbing hemorrhage in the upper portion of the right retina temporally close to a small venule; the adjacent peripheral veins were sheathed. Figure 2 is a drawing of the same eye in March, 1958, showing in the upper temporal quadrant many new venules peripherally. There is a small unabsorbed hemorrhage straddling a branch of the

Fig. 3.—Eales' disease, November, 1953, showing neovascularization nasally.

Fig. 4.—Same eye, January, 1957, showing intraretinal hemorrhages nasally and temporally.

upper temporal vein in the midperiphery and fairly extensive perivascular sheathing of the lower branch of the vein in the extreme periphery. Alongside the upper nasal vein in its periphery there is a fairly extensive black choroidal pigmentation, around which there is a perivascular sheathing. This patient has been receiving subconjunctival injections in this eye over the past three years and has had 15 such injections. The condition is considered active at the present time.

Figure 3 shows the eye of a man, now aged 44, who has been under observation for the past 13 years (Case 20 in my previous report [1]). The drawing was made in November, 1953, and shows numerous whorls of capillaries and neovascularization nasally in the left eye. He has received four subconjunctival injections of hydrocortisone during the past year. Figure 4 shows the numerous intraretinal hemorrhages nasally and temporally prior to the commencement of subconjunctival hydrocortisone therapy. The condition is still active, and he is under treatment at the present time. The hemorrhages in the temporal retina were first noted in May, 1948, and so far there have been no vitreous hemorrhages in the left eye. The vision in the right eye had been lost some years previously because of massive recurrent vitreous hemorrhages.

Figure 5 shows the eye of a 45-year-old man who has been under observation for seven years. In 1951, he was admitted to hospital for massive vitreous hemorrhage in his right eye. The drawing shows the condition of the retina in the left eye in April, 1955, and indicates perivascular

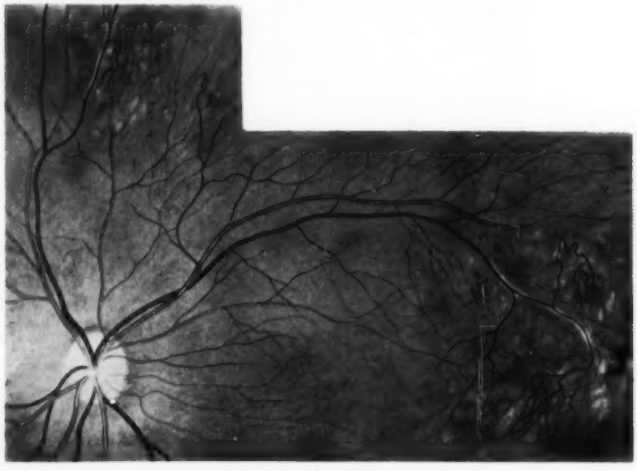


Fig. 5.—Eales' disease, left eye, April, 1955, showing perivascular sheathing and intraretinal hemorrhage.

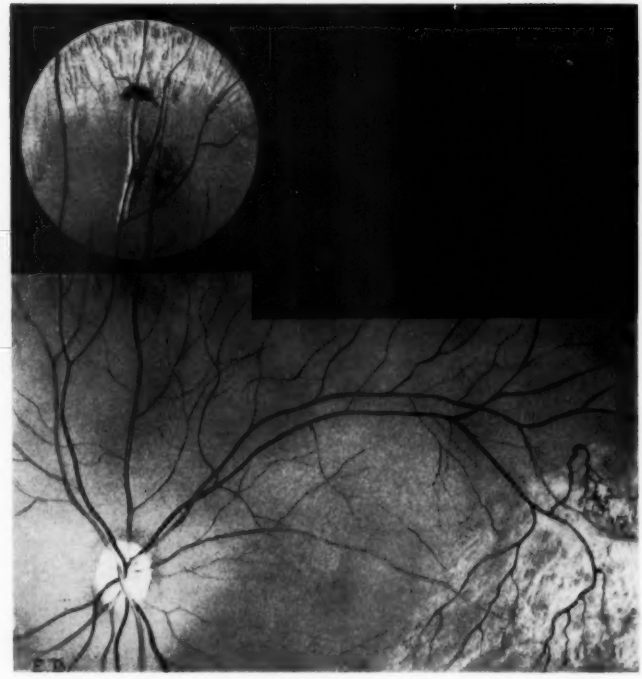


Fig. 6. — Same eye, November, 1957, indicating new hemorrhages superiorly.

sheathing and whorls of the upper temporal veins, distal to which there are newly formed venules, one superiorly and the other inferiorly. Midperipherally, there is a partly absorbed hemorrhage in the retina, while in the upper nasal retina there is marked narrowing of the peripheral veins with slight perivascular sheathing and newly formed venules. Figure 6 shows the same eye in November, 1957, and indicates no great change in the condition of the disease, excepting that a new hemorrhage has appeared superiorly in the upper nasal quadrant and there are many dilated aneurysmal venules peripherally toward 3 o'clock. This patient has had subconjunctival injections every two or three months for the past three years and has received approximately 12 such injections. It is proposed to continue the treatment because the condition is still active. There is no useful vision in the right eye which has been lost because of massive recurrent vitreous hemorrhages seven years ago.

Figure 7 (Case 23 in my previous report [1]) shows the eye of a man, now aged 45, who has been under observation for seven years. The left eye has been receiving

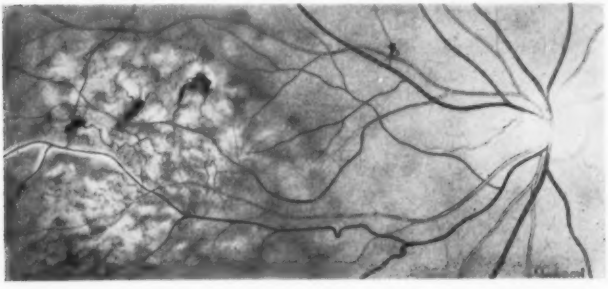


Fig. 7.—Eales' disease, left eye, June, 1955, showing numerous dilated venules nasally.

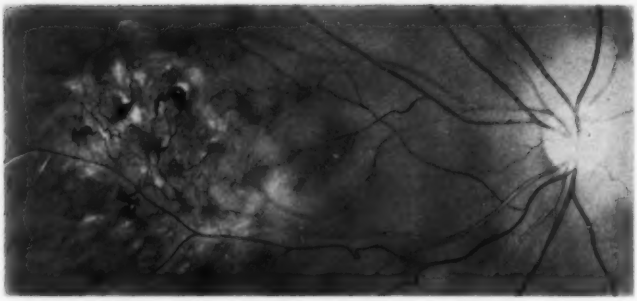


Fig. 8.—Same eye, February, 1957, showing marked aneurysmal dilatation of nasal veins.

subconjunctival injections of hydrocortisone for the past two years, and he has had six injections to date in this eye. The eye in June, 1955, showed numerous whorls of dilated venules around which exudation was present in the lower nasal quadrant, but no hemorrhages were noted. There is marked perivascular sheathing toward the periphery of the lower nasal vein. Figure 8 shows the same eye in February, 1957, and Figure 9, in February, 1958. Figure 10 is the patient's right eye in December, 1953, prior to the commencement of hydrocortisone therapy subconjunctivally. He had previously had two diathermy operations on the temporal retina of this eye 12 months before, but this did not prevent the occurrence of several large vitreous hemorrhages subsequently. During the past four years, he has had 13 subconjunctival injections

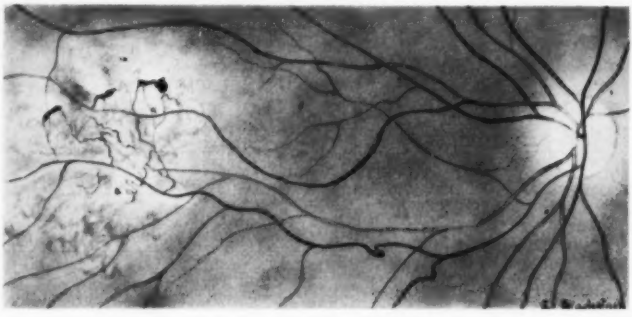


Fig. 9.—Same eye, February, 1958.

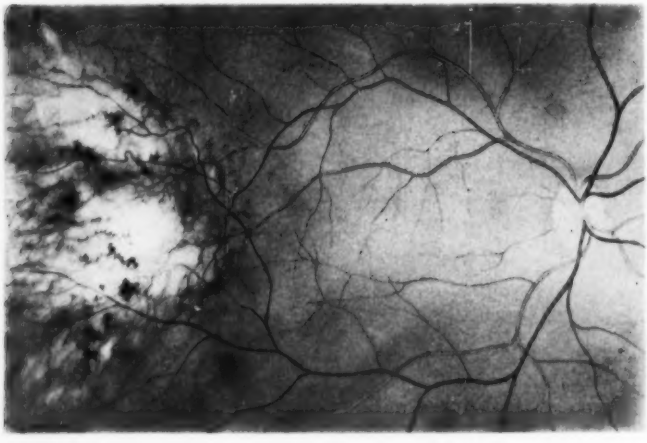


Fig. 10.—Same patient, right eye, December, 1953, indicating marked peripheral exudation.

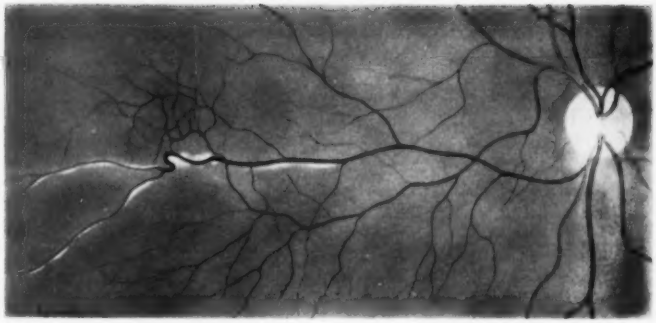


Fig. 11.—Eales' disease, left eye, December, 1953, showing marked perivenous sheathing.

Fig. 12.—Same eye, December, 1954, indicating hemorrhages more peripherally.

of hydrocortisone in the right eye; because of no further hemorrhages in the retina, the condition is considered to be inactive and treatment has been stopped for the right eye but is being continued in the left eye. The vision is correctable to 20/20 in each eye.

Figure 11 (Case 14 in my previous report[1]) is a man now aged 38, who has been under observation for 12 years. The drawing is of the eye in December, 1953, and indicates perivascular sheathing in the lower nasal vein extending into the periphery with looping of the vein. Figure 12 shows the same eye in December, 1954, at which time hemorrhages in the retina were apparent more peripherally. Figure 13 shows the eye in March, 1958, indicating that activity is still present, in view of the hemorrhages in the extreme periphery of the lower nasal quadrant. This patient has been receiving subconjunctival injections of cortisone in both eyes, in the right eye for the past four years and in the left eye for the past year and a half, a total of 18 injections in the right eye and 4 in the left eye. In July, 1955, six weeks after having received a subconjunctival injection of hydrocortisone in the right eye, he suddenly developed a vitreous hemorrhage and was admitted to hospital for bed rest and corticotropin (ACTH) therapy intravenously for a 10-day period. There has been no further vitreous hemorrhage in either eye,

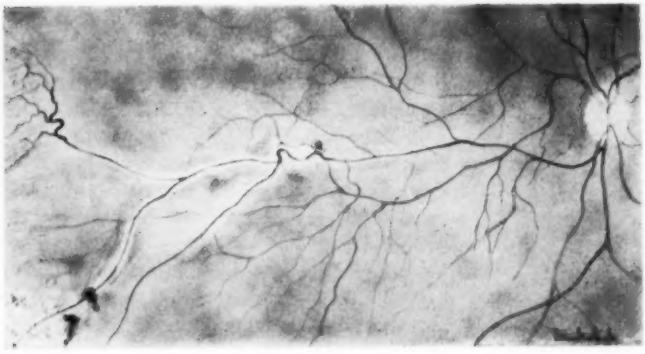


Fig. 13. — Same eye, March, 1958, indicating hemorrhages present in peripheral and lower nasal quadrant.

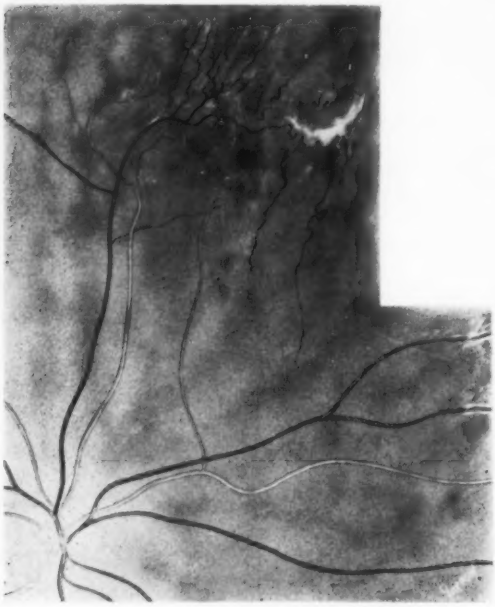
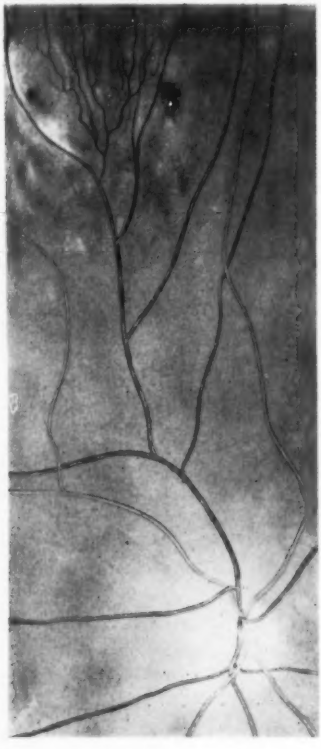


Fig. 14.—Eales' disease, left eye, December, 1955, indicating extensive neovascularization peripherally.

Fig. 15.—Right eye, December, 1955, showing hemorrhages superiorly.



and at the present time the vision is 20/20 in each eye. Treatment is to be continued because of activity at the present time.

Figure 14 shows the eye of a 30-year-old man who first had a vitreous hemorrhage in his left eye in 1943 and was hospitalized at that time for one week. The drawing shows the left eye in December, 1955, and indicates the extensive neovascularization in the upper part of the retina. Figure 15 shows the hemorrhages superiorly in the retina of the right eye. He was placed on subconjunctival injections of hydrocortisone every two or three months in both eyes in May, 1955, and continued with this treatment until May, 1957, at which time he moved to a distant city and treatment was discontinued. However, a large vitreous hemorrhage occurred in the left eye in December, 1957, and Figure 16 shows the resolving hemorrhage in the vitreous and retina superiorly in the left eye. The condition is considered to be active in both eyes, and treatment will be continued with subconjunctival injections in both eyes.

Two patients did not continue with treatment, and both of these cases had spontaneous vitreous hemorrhages. The first case is

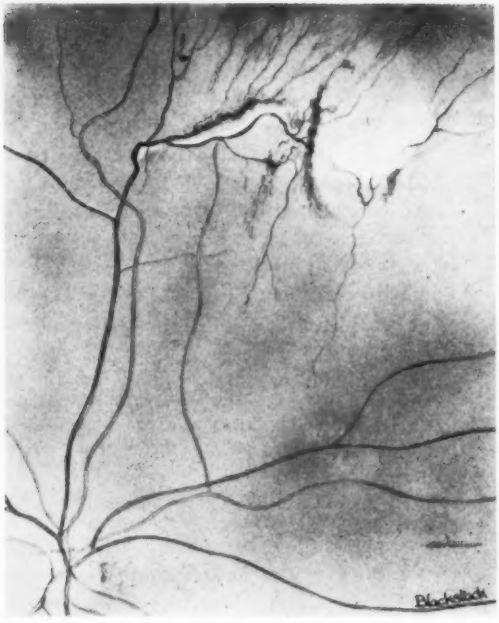


Fig. 16.—Left eye, May, 1958, showing retinitis proliferans after vitreous hemorrhage.

that of a 30-year-old man mentioned above under Figures 14, 15, and 16. The second one was a nurse (Case 10 in my previous report [1]) who had been under observation for over five years and reported sporadically for treatment, usually after having had a massive hemorrhage into the vitreous of the left eye. However, on one occasion in November, 1954, three days after an injection of hydrocortisone acetate she had a massive vitreous hemorrhage. It was felt that the absorption of the corticosteroid was probably not maximum by the third day. She has not returned regularly for treatment. When a vitreous hemorrhage occurred, the patient was admitted to hospital for complete bed rest and daily intravenous infusion of 20 I. U. of corticotropin or a comparable dose of a long-acting intramuscular preparation.

Numerous reports have appeared in the literature advocating the use of surface diathermy for the treatment of Eales' disease, both as a prophylactic measure and also as an active therapeutic measure. The largest series receiving surface diathermy coagulation for this condition was reported in 1954, by Franceschetti and Forni [4] who operated on 13 eyes with retinal periphlebitis. Vail [5] is of the opinion that diathermy coagulation promises the only treatment available in checking the recurrent hemorrhages of the vitreous, and he has observed three successful cases where this procedure was followed. However, Case 23 in my 1954 series [1] had previously had two surface diathermy operations with no improvement and subsequent recurrent vitreous hemorrhages. Since then he has been on continuous hydrocortisone therapy subconjunctivally, and during the past four years he has had no further vitreous hemorrhages. The retinal hemorrhages in the right eye have disappeared, so the treatment has now been discontinued in this eye. It is being continued in the left eye because of retinal hemorrhages, although he has had no vitreous hemorrhage in the left eye.

The specific antituberculous drugs do not seem indicated, such as thiazolsulphone (Promizole), streptomycin, aminosalicylic acid and isoniazid, because of the apparent lack of active bacterial tuberculous infection in Eales' disease. Hogan,[6] in a personal

report, has recently completed a long-term study with antituberculous therapy in eight cases, without any improvement. Two patients in my 1954 report were hospitalized for several months while treatment with these drugs was carried out, but this did not prevent further vitreous hemorrhages.

The criteria of activity which has been followed is the occurrence of new hemorrhages in the retina or spontaneous vitreous hemorrhages. At times it is difficult to differentiate between partly absorbed retinal hemorrhages and peripheral varicosities in the veins. There is no doubt that spontaneous permanent cessation of the hemorrhages does occur, and this has been observed in a number of patients followed for several years. In some patients the period of activity with retinal hemorrhages is relatively short, for example, 6 or 12 months in one eye, while in the other eye hemorrhages have been observed in the retina for as long as 10 or 12 years without a spontaneous occurrence of vitreous hemorrhages.

Summary and Conclusions

Since my previous report [1] on 31 cases of Eales' disease, an additional 24 cases have been observed, making a total of 55 cases. The clinical history and findings were so similar in all cases that I conclude that the disease results from a hypersensitivity reaction in the walls of the peripheral retinal veins in patients who have been sensitized to the tuberculoprotein.

Thirteen of these patients have been under continuous therapy with subconjunctival injections of cortisone and hydrocortisone acetate, 1 cc. (25 mg.) being injected subconjunctivally every two or three months. The period of injections ranged from one to four years in this series.

Of the 13 cases in this series, 10 have had no complication or further signs of progression of the disease. One case had a spontaneous vitreous hemorrhage six weeks after a subconjunctival injection of 1 cc. of hydrocortisone. Two other patients who did not maintain treatment had one or more vitreous hemorrhages.

* Miss E. Blackstock, Medical Art Department, University of Toronto, made the fundus drawings and the Medical Art Department, Sunnybrook Hospital, Toronto, supplied the photographic reproductions of the fundus drawings.

Department of Ophthalmology, Banting Institute, University of Toronto (5).

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The Multiple-Pattern Method of Visual Field Examination

A Five-Year Evaluation of Its Effectiveness as a Visual Field Screening Technique

DAVID O. HARRINGTON, M.D., and MILTON FLOCKS, M.D., San Francisco

Since its first presentation before the American Ophthalmological Society,[1] in 1953, the multiple-pattern method of visual field examination has been widely accepted and used in clinics and in private practice. It has proved to be an effective technique for visual field screening in mass examinations of personnel in industry, in the armed forces, in driver-testing, and in glaucoma-detection surveys in various parts of the country. There is now a considerable literature on the method.

Much data has been accumulated through personal communication with a large number of the more than 500 users of the visual field screener. Some of this material was collected in response to a questionnaire. Numerous unsolicited reports have been submitted by users who attested to the accuracy and speed with which the method was able to detect a wide variety of visual field defects, later confirmed by standard perimetric techniques.

We have considerably enlarged our experience with the method. We have used it as an initial test for the detection of field defects and also to confirm the findings in cases with known field loss. New patterns have been designed to cover the visual field better, to reduce the incidence of false-positive responses, and to increase the sensitivity and reliability of the test. Further experimentation is continuing, and we have every reason to feel that our original estimate of the value of the method was sound.

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From the Division of Ophthalmology, University of California School of Medicine, the Department of Ophthalmology, Stanford Unversity School of Medicine, and the U. S. Veterans Administration Hospital.

Review of Literature

After our preliminary report on the visual field screener, we improved the patterns and their method of presentation. After collecting further data from clinic and private practice and at an exhibit at the American Medical Association meeting in San Francisco, in June, 1954, we presented this material to the American Academy of Ophthalmology and Otolaryngology. This was published in the transactions of the society [2] and simultaneously in *The Journal of the American Medical Association* [3] in 1955.

One of the first and most enthusiastic advocates of the multiple-pattern method of visual field examination was Dr. Hedwig Kuhn, Secretary of the joint committee on Industrial Ophthalmology of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology. Dr. Kuhn immediately began to work on collecting material on the efficacy of the screener in her private practice and introduced the method to a number of industrial surgeons in her area for use in long-term health screening programs in industry with particular reference to glaucoma detection. Dr. Kuhn has presented the method to the Industrial Medical Association [4] in this country and to similar organizations in Finland and Australia.

In 1955, Dr. Logan Robertson, an industrial physician and consultant in Occupational Health Services, began a 12-month

study of the visual field screener. His mobile medical units examined 7,821 employees in seven different industrial plants. He reported his results to the American Academy of Ophthalmology and Otolaryngology[5] in 1956. The multiple-pattern field screener part of his comprehensive general physical examinations required from two to five minutes to perform. The over-all yield of abnormal responses was approximately 5%. The incidence of abnormalities in men was greater than in women, and there was a marked increase with advancing age. Twenty-five per cent of the abnormal responses in men showed recognizable "patterns" in the type of field loss, as against 14% in women. Some of these recognizable defects were listed as quadrant defects, bilateral and unilateral; concentric narrowing; homonymous hemianopsia, and central visual defect. Bilateral defects outnumbered the unilateral ones to a statistically significant degree. Dr. Robertson concluded that the multiple-pattern field screener is a rapidly administered test adaptable for use in large population screening, but he predicted a high incidence of referrals unless the test were conducted with care and patience. We recommended retesting techniques on the screening level to decrease these false-positive tests.

Vaughan[6] used the visual field screener in his glaucoma detection survey of 1,000 hospital patients in 1955. He found an incidence of 1.9% of glaucoma by various methods of examination. Of these 19 patients, the majority had visual field defects, all of which were detected by the visual field screener and subsequently confirmed by standard perimetry.

Roberts[7,8] reports the use of the multiple-pattern tachistoscopic visual field screener in 1,500 consecutive office and clinic patients and correlates the results with tangent-screen perimetry. Included in these 1,500 examinations were tests on 67 previously known glaucoma cases and on 33 cases suspected of having glaucoma. There were 133 patients who showed abnormal responses to the multiple-pattern test. Of these, 39 were in the group of known glaucoma cases, 31 were in new glaucoma cases, 23 showed other ocular or central nervous system pathology, and in 40, the pathology was undetermined or the tests were false positives. All of the known and suspected glaucoma cases and all patients with abnormal multiple-pattern responses were then studied by standard central field techniques using the 1/1,000 isopter.

The results of these correlative tests indicated that "the multiple pattern tachistoscopic method for visual-field testing is not only a quick but also a sensitive and accurate tool in glaucoma work. Especially in glaucoma, where the field changes are slight to absent and often changing, the tachistoscopic method appears to be nearly as sensitive as standard central field techniques using the 1/1,000 white isopter, and correspondence between methods is somewhere between 80% and 90%, as judged from this relatively small series. It is only in the equivocal cases, which are often equivocal because of poor patient reliability, that the correspondence between the techniques becomes less."

Sloan[9] has satisfactorily explained the reason for the difficulty, reported by us,[2] encountered in testing aphakic patients with the multiple-pattern method. She recalls that the crystalline lens does not transmit ultraviolet light, and therefore in the aphakic patient the filtering action of the removed lens must be supplied by a Wratten No. 2A filter if the patient is to see the test pattern as the normal patient does. Without the filter there is insufficient contrast for the aphakic patient to respond correctly.

Danielson,[10] in a very comprehensive study of the relationship of fields of vision to safety in driving, compared the multiple-pattern method of visual field examination with a number of other field-screening devices used in driver testing. He concluded that "the best screening apparatus yet offered to measure the central fields of drivers quickly is the Harrington-Flocks Multiple Pattern Method." As constructed, however, he felt that it tends to give too

high a percentage of false positives in drivers' examinations and made the following suggestions:

"A. That it be done in an evenly and dimly lighted room away from extraneous influences and without haste.

"B. That the instrument be modified for specific situations by making fewer patterns, using larger stimuli and designing the patterns with a view of uncovering the quantity of field loss rather than giving hints as to diagnosis."

Havener,[11] in discussing glaucoma screening, lists the criteria for ophthalmologic referral of cases among which he places visual-field loss as a late sign of glaucoma. He states that the multiple-pattern visual field screener "is a very good test which effectively detects the presence of a variety of diseases causing field defects. Unfortunately it cannot detect the earliest stages of glaucoma, when elevation of pressure is the only abnormality. Nevertheless, the Harrington Screener has established itself as a valuable, quick, simple screening test for eye disease."

Zugsmith,[12] after commenting on the superiority of luminescent test objects activated by ultraviolet light as advocated by one of us (D. O. H.),[13] has modified the Harrington-Flocks screener for use as a magnetic campimeter. He states that the multiple-pattern examination can be performed by a nurse or technician, followed, when indicated, by quantitative perimetry by the ophthalmologist. He believes that the multiple-pattern examination "requires little more time than confrontation fields and has inestimably more value."

Zugsmith[14] uses a flocced, nonferrous top on the Harrington-Flocks screener, with tangent screen markings for 330 mm. on the back. Magnetic test objects are easily constructed by cementing luminescent targets of varying size to thumb-tack heads which are moved about by application of a magnet to the back of the screen.

Vail, in his review of "The Visual Fields,"[15] by one of us (D. O. H.), in which the multiple-pattern method is described, has pronounced it "excellent."

Hilton,[16] in an article prepared for publication in an optometric journal, has reported a visual field survey of 607 persons composed of Army personnel and their dependents presenting themselves for routine eye examination at an Army hospital. Nineteen (3.1%) of these failed the test and were referred for complete eye examination including tangent-screen study. Three of these failures were not confirmed, yielding an over referral rate of 15.8% but a false-positive rate of only 0.5%. The remaining 16 patients showed a wide variety of diseases and visual field defects, including a number with small peripheral scotomata, a type of visual field defect which is admittedly difficult to detect by any method of perimetry without foreknowledge of the lesion producing it. Other abnormalities included hemianopsia with optic nerve injury, two cases of hysteria, and assorted retinal, choroidal and optic nerve lesions. The author is properly concerned that the screener should be used to supplement and not supplant standard quantitative perimetry.

In discussing referral rates for more definitive study of the visual field by quantitative perimetry, Hilton presents the results of four previous series of cases and notes what he considers a rather wide range of over-referral or false-positive tests. He points out that "a moderate over-referral rate may be regarded as a good thing, a margin of safety, but that under-referrals tend to provide the patient with a false sense of security." He considers the under-referral rate of greater importance than the over-referral rate in terms of public health and suggests that its further elucidation would be of value. The author suggests a method of quantifying the test which should decrease both over-referral and under-referral.

Horsley, Lewis, and Packer,[17] in a glaucoma detection survey of 1,210 outpatients over 40 years of age, concluded: "The Harrington-Flocks visual screening test

shows promise as an instrument for mass screening for defects in central visual fields in view of its greater specificity and its reasonable sensitivity when compared to tangent screen tests which are more time-consuming and fatigue-producing."

Personal Communications

In the discussion of Robertson's paper,[5] one of us (D.O.H.) quoted a number of personal communications from users of the multiple-pattern method of visual field examination, citing their experience with the method and attesting to its value as a screening device. While these studies have not been published, they represent a considerable volume of statistical data compiled by independent and unbiased observers, and as such they should be included in this review.

Dr. T. F. McGough, Director of Public Health for the City of Alexandria, Virginia, has used the multiple-pattern visual field screener as part of a long-term sight conservation program in that city. The results of two of these surveys were reported[18] to us in February, 1956, as follows:

1. A total of 4,968 persons were tested in two separate multitest screening programs.

2. Approximately 5% of the adult population in this area will fail the multiple-pattern visual field test if an average of less than four minutes per person is used in the preliminary screening. (Our original recommendation was for four minutes.)

3. This figure of 5% can be reduced to a more realistic and accurate figure of 2% if an opportunity is provided for a secondary screening in a separate room before the person leaves the building on the same day.

4. Out of 47 persons who twice failed the visual field screening, ophthalmologic confirmation was obtained on 43, or 91.5%.

In further communications[19] Dr. McGough states that "in our opinion Dr. Harrington does not over-estimate the Visual Field Screener" and "in our hands the Screener has done everything that Dr. Harrington has claimed it will do."

Colonel J. H. King Jr. reported[20] that he had processed some 5,000 routine patients and 50 complicated cases. He stated, "there is no question about the overall value of this screener," but felt that the test cards should be of more stable construction.

Before establishing the multiple-pattern method as a routine test in his clinic at the University of Chicago, Dr. Frank Newell[21] examined 150 patients with known visual-field defects with the screener. In only one case did the screener fail to detect a field defect previously found on the tangent screen, and this was a small paracentral scotoma due to an area of healed choroiditis between the macula and the optic disc. The screener is now used as a routine test on each patient entering the clinic.

Dr. F. Bruce Fralick[22] states, "We have enjoyed using this apparatus routinely when the patient's history is taken. On occasion we have found changes which would indicate other perimetric methods which most likely would not have been done except for this original screening."

Dr. William B. Clark[23] comments that he finds the screener the "most effective method of visual field screening that has been devised so far." He correctly emphasizes that it should be used "for a screening device only and not as a substitute for quantitative perimetry."

In the past few months another instrument using the same principal has been advertised in the optometric journals as a "Multiple-Target Screener." This instrument is an obvious copy of the one designed by us and manufactured under license by the Jenkel-Davidson Optical Co., of San Francisco.

We have examined this instrument and find it in many ways inferior to our own in the matter of illumination, color, brightness and duration of stimulus, and pattern design.

Clinical studies on patients with known visual field defects demonstrate that this instrument does not compare in sensitivity to our own.

We wish it to be understood that we have no responsibility for the design or manufacture of this instrument. We fear that this instrument or others of inferior design and quality may discredit the multiple-pattern method of visual field examination.

Questionnaire

In 1957, a questionnaire was sent to 380 known users of the multiple-pattern screener. Although there are many more than this number of screeners now in use, their location is unknown to us if they were purchased through their local instrument jobber.

It was felt that the experience of a cross section of the users of the screener might shed valuable light on the possible success or failure of the method aside from those experiences reported in the literature.

One hundred eighty questionnaires were returned with enough data to be of statistical value. A number of physicians returned the letter even while noting that they felt their experience was too limited to be of value. These were not used. Twenty responses were received from optometrists. Eighty persons took the trouble to write personal notes, some of which will be quoted below and many of which will be helpful in improving the method in the future. The responses were from all parts of the country. Most answers indicated use of the screener in the private practice of ophthalmology. Not every question was answered by each person.

The following questions were asked, and the answers are tabulated.

1. Was there any difficulty in understanding, conducting, or recording the test?
   - (*a*) Yes 16 (9%)
   - (*b*) No 110 (61%)
   - (*c*) No answer (30%)
2. In what percentage of patients do you use the screener routinely?
   - (*a*) 100% 22 (12%)
   - (*b*) 75% 28 (16%)
   - (*c*) 50% 35 (19%)
   - (*d*) 25% 40 (22%)
   - (*e*) 10% 3 (1%)
   - (*f*) No answer (30%)
3. When the test indicates the presence of a field defect, do you
   - (*a*) perform perimeter or tangent screen examination?
     Yes 117 (65%)
   - (*b*) refer patient for perimetry?
     Yes 7 (3%)
   - (*c*) accept test without further examination?
     Yes 5 (2%)
   - (*d*) No answer (30%)
4. In what percentage of patients do you find that visual field defects detected on the screener were also found on tangent-screen examination?
   - (*a*) 100% 25 (13%)
   - (*b*) 95% 7 (3%)
   - (*c*) 90% 55 (30%)
   - (*d*) 50% 4 (2%)
   - (*e*) 25% 4 (2%)
   - (*f*) No answer (50%)
5. Estimate your percentage of false-positive tests (i. e., screener indicated a field defect but none was found by perimetry).
   - (*a*) 0% 15 (9%)
   - (*b*) 5% 40 (22%)
   - (*c*) 10% 32 (18%)
   - (*d*) 15% 9 (5%)
   - (*e*) 20% 8 (5%)
   - (*f*) 25% 11 (6%)
   - (*g*) More 3 (1%)
   - (*h*) No answer (34%)
6. In what age group do false-positive tests most commonly occur?
   - (*a*) 5-10 yr. 9 (5%)
   - (*b*) 10-20 yr. 4 (2%)
   - (*c*) 20-40 yr. 0 (0%)
   - (*d*) 40-60 yr. 17 (10%)
   - (*e*) Over 60 yr. 68 (37%)
   - (*f*) No answer (46%)
7. Has the screener missed any field defects which were later found by perimetry?
   - (*a*) Yes 34 (19%)
   - (*b*) No 80 (44%)
   - (*c*) How many? Very rare to 20%
   - (*d*) No answer
8. Is there good correlation between multiple-pattern method and perimetry as regards:
   - (*a*) location of field defect?
     Yes 115 (63%)
     No 2 (1%)
     No answer (36%)
   - (*b*) size of field defect?
     Yes 59 (32%)
     No 40 (22%)
     No answer (46%)
   - (*c*) diagnosis of disease?
     Yes 67 (37%)
     No 21 (12%)
     No answer (51%)

9. Have you found the screener of value in:

(*a*) glaucoma detection?		
Yes	82	(45%)
No	27	(15%)
No answer		(40%)
(*b*) diagnosis of neurological disease?		
Yes	104	(57%)
No	8	(3%)
No answer		(40%)
(*c*) explaining visual field defects by other tests?		
Yes	45	(25%)
No	32	(18%)
No answer		(57%)

Personal comment and criticism was invited and elicited 80 responses which varied greatly and in many instances indicated thoughtful study and evaluation of the method. Some suggestions have already been adopted for the improvement of the instrument, and others will be incorporated in future models.

A few of the more interesting comments are as follows:

1. "The more the method is used, the more valuable it becomes."

2. Three persons commented on the value of the method in testing uncooperative or senile patients who would not maintain fixation on the tangent screen, and one well-known perimetrist stated that it was particularly effective in examining "stupid" patients.

3. A neurosurgeon finds the screener "a valuable, rapid and entirely practical adjunct in routine neurological examination. In a busy practice it is surprisingly accurate."

4. At least 10 users of the method stated that its greatest value was to stimulate more perimetry. Several persons remarked that it had revived their interest in visual field study by detecting disease processes which they felt certain they would have missed.

5. Four writers stressed the value of the method as a screening device but were more concerned lest it supplant quantitative perimetry in some offices. This view has been emphasized by us. We urge its use as a screener in order to stimulate more frequent perimetric examination and not as a means of avoiding visual field study by standard methods.

6. Several correspondents were enthusiastic about the method as a glaucoma-detection device and stated that several cases were revealed which had eluded them in previous examinations. One optometrist referred four patients to ophthalmologists with diagnoses of glaucoma which were subsequently confirmed. Others felt that the method was more efficient in detecting neurological disease than in finding glaucoma. Five comments urged the publication of a separate pattern series specifically designed for glaucoma detection. A special pattern series is already being tested on known glaucoma patients.

7. Extremes of praise and condemnation of the method were recorded in such comments as those which follow:

(*a*) "Second only in value to my slit lamp and ophthalmoscope. Test should be a part of every refraction."

(*b*) "Kindly send someone to pick up this instrument. We have never used it and don't know how."

(*c*) "Feel that screener is the best office instrument I have. The M. P. method has stimulated my interest in perimetry so that I have redesigned my office to give more space and time to visual field examination."

(*d*) "Too many false positive tests. Don't use method any more."

It will be noted that these comments took many forms. Some were suggestions for improving the method, and insofar as they are practical they will be adopted. We are grateful for the interest which stimulated them. Some were critical, and this five-year evaluation is, in part at least, an answer to such criticism. No comments were more welcome than those which indicated an interest in quantitative perimetry and visual field study directly attributable to the use of the multiple-pattern visual field screener. If the method can stimulate a sustained interest in perimetry, it will have served its major purpose—the examination of more visual fields.

Independent Investigation

We have not depended entirely on the work of others for data for this survey. We have continued to study every available patient with a visual field defect for comparison of their responses to tangent screen perimetry with those to the multiple patterns. In the vast majority of cases there has been very close correlation between the two methods.

As with any other method of subjective examination, experience with the field screener contributes much to its accuracy. We agree with Danielson [10] and McGough [18] that the test should be conducted in a quiet room and that attention should be paid to the comfort of the patient, lighting of the cards and avoidance of shadows, explanation of the test, and position of the examiner so that he can watch the patient's fixation. To minimize false-positive tests, those persons whose responses indicate a visual field defect should be reexamined on the screener, and if there is still doubt, a tangent-screen examination is indicated.

To those who complain that the method yields too high a percentage of false positives, we would say that we are aware of the false positives and have attempted to correct this defect by the design of Pattern Series II and III. However, it is not the false positives but the false negatives which should worry us, and in this regard we would point to two cases from our own experience:

CASE 1.—A patient whose multiple-pattern test indicated a bitemporal hemianopia was then examined on perimeter and tangent screen with negative results and labeled as a false positive. Sometime later he first noted visual loss, and again his multiple-pattern test showed bitemporal field loss. This time there was confirmation on the tangent screen, and eventually the surgical removal of a pituitary adenoma was accomplished.

CASE 2.—A patient with neurologic evidence of a space-consuming intracranial lesion responded normally to tangent-screen examination but revealed evidence of a right homonymous hemianopia on the multiple-pattern screener. It was only when the tangent-screen examination was conducted with simultaneous double stimulation with 3 mm. stimuli that the character of the hemianopic field loss was demonstrated. The patient had a glioma of the postparietal area.

These two examples certainly illustrate that at times the multiple-pattern method is capable of greater sensitivity than standard perimetric techniques. There have been a number of instances of this in our experience.

On the other hand, the multiple-pattern method will fail to reveal visual field defects which are actually present. This is uncommon, and it is true of any method of perimetry. Three examples will illustrate these false-negative responses.

CASE 3.—A patient with an assumed cerebrovascular lesion of the left side with aphasia and motor involvement on the right revealed a homonymous hemianopia on the right in the 5/1,000 isopter but gave normal responses on repeated testing with the multiple-pattern method. Examinations were conducted by two ophthalmologists on several occasions with the same result, and we are unable to explain this false-negative response. It is the only such example in a large series of correlated studies with the multiple-pattern and tangent-screen methods.

CASE 4.—A homonymous hemianopia involving only the peripheral field beyond 30 degrees was missed by both the tangent-screen and the multiple-pattern method and subsequently detected on the arc perimeter in the 2/330 isopter. Continued search for the field defect was justified by the presence of papilledema and visual hallucinations. The lesion was a metastatic carcinoma involving the anterior portion of the calcarine fissure.

CASE 5.—A patient with established open-angle glaucoma with elevated intraocular pressure and abnormal optic discs gave normal responses to the multiple-pattern method. Tangent-screen examination showed a peripheral nasal depression and a narrow

nerve fiber bundle defect in the superior field in the 2/1,000 isopter. With further progression of the field loss, the defect was revealed in the multiple patterns.

A few examples of this type have been encountered, but for the most part the established glaucoma field defect is readily detected with the multiple patterns.

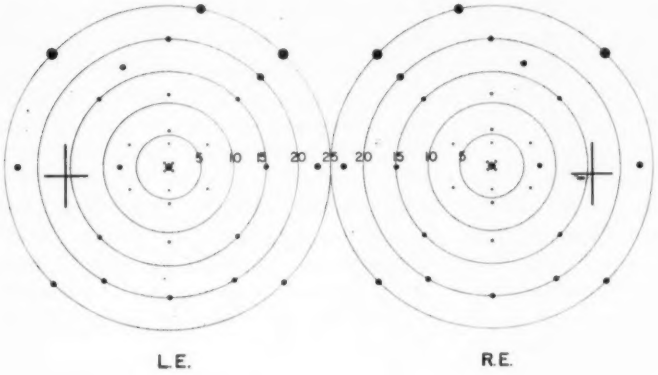
It should be emphasized that all glaucoma suspects should have the benefit of the most careful perimetric study and that the role of the multiple-pattern method in glaucoma detection is only to stimulate more definitive visual field examination by making available a rapid method of testing to those patients who would otherwise have no perimetric examination whatever. Not all established glaucoma is accompanied by a loss of visual field. Some glaucoma cases reveal visual field defects only to the most careful and tedious quantitative analysis. These patients may, of course, respond normally to the multiple-pattern test.

We have been concerned about the possibility of false-negative responses in glaucoma. To this end we have experimented with a series of patterns specifically designed to detect the types of visual field defects most often encountered in glaucoma.

There is no doubt that these patterns will detect a larger percentage of the early field defects in glaucoma, but by the same token, because the stimuli are smaller and the patterns somewhat more complicated, there will be a higher percentage of false-positive tests. The examination using these patterns requires a little more time, and more of the tests require repetition when certain stimuli are missed. This tends to decrease the value of the test as a screening device by decreasing the number of persons who can be examined in a given unit of time. These patterns, specifically designed for the earlier detection of glaucoma field defects, will be published as a separate series which may be substituted for the standard Series III in the box of the screener. Before releasing them, however, it is our purpose to test them on a larger number of glaucoma patients. It is necessary, by careful experimentation, to determine the most efficient pattern design and at the same time to avoid complicating the test to the point where it ceases to be a screening method and loses its advantages over standard perimetric techniques. This emphasizes again our insistence on the principle that the multiple-pattern method is not intended to supplant quantitative methods of perimetry but only to supplement them. We believe that the screener can be made to serve more accurately and efficiently in glaucoma detection but only if this principle is understood.

Our original series of 10 patterns [1,3] has been twice revised to provide more complete stimulus coverage of the field. Again a balance had to be maintained between the impossible ideal of at least one stimulus in every part of the field and the principle of simplicity which makes the method a practical and rapidly administered screening test. We experimented with more complex patterns containing more stimuli on each card so that more areas of the composite pattern were included in the test. This led to some confusion, especially in the older age group, and thus to more false-positive tests. The alternative solution of using more cards increases the bulk of the book and slows down the performance of the test by making it longer and less facile.

In Series II and III of the multiple-pattern method, which is now published and available for use in our screener, we have compromised by moving some of the stimuli and changing a few of the patterns to obtain more even distribution in the field. We have not increased the number of stimuli on any card beyond four. We have replaced lines with dots to avoid confusion and attempts at interpretation by the patient. The stimuli have been adjusted in size so that those closest to fixation are generally smaller as are those closest to the light source. This makes for greater uniformity in stimulus intensity. The number of patterns remains at 10, but the number of cards in Series II and III have been doubled. The first 10 cards are used to test the right eye, and the second 10 cards are for the left eye.



Composite of stimuli in Pattern Series III.

The patterns appear in different order in the test for each eye, making it more difficult to memorize the pattern sequence. It is unnecessary to turn back the cards for testing of the second (left) eye. This materially increases the speed of the test and discourages shift of the head and chin position between examination of the right and left eye. Minor improvements are being made in the chin rest and occluder to facilitate better and more rapid positioning of the patient's head (Figure).

We feel that the present Series II and Series III patterns are subject to still further improvement, and we are continuing our experimentation in this regard with patients with all varieties of known visual field defects. This is a slow process, and we are reluctant to make changes until they have proven more efficient than the present series. We do not believe that major changes are possible, while still maintaining the screening character of the method. We feel that Pattern Series II and III have such definite advantages over Pattern Series I that the latter should no longer be used. The new series may be obtained by writing to the manufacturer.

One of us (D. O. H.) has experimented with patterns designed to render the method more sensitive. On the basis of these experiments, we are convinced that the multiple-pattern method can be made more sensitive to minimal visual field defects than the arc perimeter and at least as sensitive as the 1 meter tangent screen for the majority of cases. In order, however, to attain this sensitivity it becomes necessary to decrease stimulus size, increase background brightness, and increase the number of patterns and stimuli so as to cover every area of the field. This immediately increases the complexity of the test and removes its unique and special advantage over the standard methods of perimetry, namely, the ease and rapidity with which it can be conducted.

There is, of course, an infinite variety of ways in which the multiple patterns can be modified, and it is possible for individual investigators to design their own pattern series for specific purposes. But it must be remembered that under these special circumstances the multiple-pattern method ceases to be a screening device and enters into competition with the tangent screen, over which it may have no superiority.

Among the modifications which we had considered was a series of of patterns designed for children. We found this unnecessary as our experience with children has been most gratifying with the standard Series I and II.

Another modification which we believe should be useful is a much simplified series of three cards for each eye for the testing of driver's-license applicants. The stimuli are relatively gross but much less gross than the confrontation test and certainly better

than no visual field examination. We have discussed the matter of visual field testing with the Division of Motor Vehicles and have been told that, while it is a desirable addition to the present method of vision testing, it would require the services of a considerable number of additional examiners if only two minutes were added to the present examination. We believe that field testing is important for drivers and that our method offers the only presently feasible way of accomplishing this. If only a very small number of bona fide visual field defects were detected and referred for definitive perimetry, it would be well worth while in the possible saving of life.

One potential of the visual field screener which has been neglected, except by Zugsmith,[14] is the use of the back of the box for standard tangent-screen perimetry. When multiple pattern responses are abnormal the visual field may be very accurately checked with a 1 mm. target without moving the patient. This is at least as accurate as the arc perimeter and much simpler. All one needs to do is affix a luminescent 5 mm. fixation target to the middle of the inside of the lid of the screener, press the switch for sustained black light illumination, and test the field with a 1 mm. luminescent stimulus held on the wand supplied with the instrument. Or, alternatively, the instrument may be modified, as suggested by Zugsmith, for the use of magnetic luminescent test objects. Whenever a patient responds abnormally to the multiple-pattern stimuli it is our practice to immediately test the area in question with a 1 mm. luminescent test object, using the lid of the screener as a short-radius tangent screen. Confirmation of the abnormal multiple-pattern response is usually quickly and accurately obtained and may then be checked by more precise quantitative perimetry.

Summary

Since the preliminary report on the multiple-pattern method of visual field examination in 1953, there have accumulated considerable data on its effectiveness as a screening device. This material is presented from review of the literature, presentation of reports through personal communication, analysis of data obtained from responses to a questionnaire, and our personal experiences and experiments.

The method is now in widespread use in clinics and in private practice and has been successfully tested in mass screening examinations in industry, the armed forces, and glaucoma-detection surveys. Independent and unbiased evaluation of the method has been obtained.

We have considerably enlarged our experience with the method and have further improved the instrument and the design of the stimulus patterns. Experiments are continuing to simplify the test still further and to increase its sensitivity. The use of Pattern Series I should be discontinued in favor of Series II or III.

There is every reason to feel that the original estimate of the value of the method is justified.

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Retinal Arteriosclerosis Secondary to Vein Obstruction

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Gunn [1] used the term copper wire to describe retinal arteries with a lighter than usual over-all color and a sharp exceptionally bright central light streak. He noted such arteries in some patients with albuminuria and in others with hypertension, and he presumed that this ophthalmoscopic appearance was due to hyaline degeneration of the arterial wall.

Ballantyne [2] stated that Sir William Gowers shortly thereafter, in an apparent misquote of Gunn, called the same change silver wire. Although silver and copper wire were therefore originally used to describe the same arterial change, Ballantyne clarified their usage today as follows: 1. Copper wire—a term used to describe beginning sclerosis of an artery. The wall becomes less transparent and the vessel pale. The artery is increased in diameter, is tortuous, and has a more brilliant central light reflex. 2. Silver wire—a term used to describe advanced sclerosis of an artery. The sheathing is irregular and pipe-stem in type, and complete concealment of the blood column by white tissue is common.

The prevalent concept of copper- and silver-wire arteries was expressed by Scheie.[3] Copper wire represented milder and silver wire indicated severer arteriolar sclerosis. These appearances were due to changes in the arterial wall after prolonged hypertension. They could appear more rapidly in severe hypertension or be pronounced in milder hypertension of long duration. At any rate, prolonged reversible arteriolar spasm eventually led to irreversible change in the arteriolar wall constituting varying degrees of arteriolar sclerosis—copper-wire and silver-wire arteries.

The overwhelming acceptance of this tenet—that arterial disease was primarily and solely responsible for these changes—has obscured the few reports suggesting other factors.

In Gunn's [1] original description he drew attention to A-V crossing defects, impeded venous circulation, venous banking, and even impending branch vein obstruction in fundi showing such copper-wire arteries. Thus, the presence of partial venous obstruction or venous stasis was known from the first, but its significance was not appreciated.

In 1936, Jensen [4] described arteriosclerosis of the artery accompanying an obstructed vein. Eight cases showed no arterial change at the time of the vein obstruction. Four to twelve months later all arteries showed sclerosis secondary to vein obstruction. Some were thin with an irregular sclerosis; others progressed to white cords without visible blood columns. Arterial walls varied from brilliant to gray and indistinct. Twelve other cases showed considerable arteriosclerosis in the affected quadrants when the vein obstruction occurred. Four months to seven years later these arteries showed more extensive sclerosis. There were silver-wire reflexes, thin and irregular blood columns, and irregular constrictions. Some arteries appeared as pale gray lines, and some segments even disappeared.

Twenty of twenty-three cases of previous tributory thrombosis showed some sclerosis of the accompanying artery, always most marked peripheral to the site of vein ob-

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Drs. Gerard DeVoe, Robert Coles, and Marvin Gillman made available case histories and permitted examination of their patients.

struction. Field examination revealed complete artery obstruction in 7 cases and patent arterial lumens in 13.

Jensen believed that the arteriosclerosis was due to transmission of the stasis in the obstructed vein territory through the capillary system to the artery. This arterial stasis caused the disturbed nutrition of the end artery wall.

In 1937, Ballantyne[2] drew attention to this same phenomenon. He ascribed straightening and narrowing with loss of arterial wall transparency to senile changes usually apparent after the age of 60. Microscopically such arteries showed endothelial proliferation and fibrosis or hyperplasia of the fibrous coat. After this he noted A-V changes in this order of frequency: bending of veins, apparent constriction of veins, and, rarely, actual constriction of veins. Such changes were seen in patients with normal or only slightly elevated blood pressure.

Ballantyne considered parallel and pipestem sheathing of arteries evidence of advanced arteriosclerosis. While he saw this in isolated cases of uncomplicated arteriosclerosis, he noted it most frequently and most pronounced after thrombosis of the central retinal vein. Such arteries microscopically showed hyaline wall changes or endothelial-cell proliferation with lipid degeneration.

He considered arteriolar sclerotic arteries to be abnormally wide and always tortuous, with inconspicuous variations in caliber. They showed a bright axial reflex and a copper-wire appearance. The perimacular arterioles were irregular and tortuous; the veins were full and tortuous with increased reflex, and all types of A-V defects were present. Microscopically, in the late stages of such arteriolar sclerosis, necrotic and thrombotic changes in the finest arterioles were demonstrated. He drew attention to the fact that these increased arterial changes appeared at the same time as increased venous congestion. Ballantyne corroborated Jensen's findings and noted that arterioles were not necessarily blocked where the blood column was hidden.

Finally, he believed that variations in caliber after arterial obstruction appeared too soon after the obstruction not to have been present but unapparent before. He believed these changes became much more manifest when the artery was partially refilled under a lower pressure than before the obstruction.

Thus Ballantyne established the facts that silver-wire arteries occurred in the absence of hypertension, that such changes occurred simultaneously with increasing venous congestion, and that such arterial change was most frequent and marked after actual obstruction of the central retinal vein.

Lister and Zwink[5] mentioned narrowing and sclerosis of the artery and even its complete obliteration after obstruction of the accompanying vein, but they did not describe these changes further.

Leishman[6] described the same arterial changes as are under discussion in this paper. He attributed them to a "seeding" of an atheroma into a more peripheral arteriole. However, his Figure 39 (*a* and *b*) shows the changed arteriole lying between two dark, dilated, and tortuous veins which even show mild beading in the later photograph (*b*). Certainly this is an arteriole lying in a retinal area of venous stasis.

His Figure 40 (*b*), considered by the author to be a partial occlusion of the central retinal artery, appears to me as a classic stasis central retinal vein obstruction. Shown were edema of the disc; dark, dilated, and slightly tortuous veins; blot hemorrhages in all quadrants, and particularly small hemorrhages predominantly about the fine peripheral venous twigs. Furthermore, the "slight recovery of vision" is more in keeping with central retinal vein obstruction than central arterial block.

In his Figure 41 (*a*) the classic secondary arteriosclerosis of the inferior temporal artery is accompanied by the most dilated and darkest vein in the photograph, the vein also showing a halo sheathing so typical of previous venous obstruction or ve-

nous stasis. I would therefore interpret this as arteriosclerosis developing because the artery was lying in an area of venous stasis rather than as peripheral arteriosclerosis secondary to "seeding" from the obstructed central retinal artery.

Of particular note was Leishman's statement that "in histological sections taken from cases of severe and fulminating hypertension, the venous picture is often more striking than the arterial picture." Endothelial-cell proliferation in veins with masses of fused platelets adhering to some such cell accumulations certainly indicated a previously unappreciated degree of venous stasis and blockage in hypertensive retinopathy.

Salus [7] stressed Guist's sign in hypertension: narrowed macular arterioles and dilated tortuous corkscrew macular veins. To this he added capillary aneurysms, small hemorrhages, sheathing, and slight pigment changes, all in the macular area. Salus also sometimes noted smaller degrees of these same macular changes in "senile fovea" occurring after the age of 50.

Except for the macular arteriolar narrowing, undoubtedly due to hypertension, all of the above changes have been shown to be secondary to obstruction of one or more veins draining this area.[8]

Recently, Quiroz and Sauter [9] described retinal arteriosclerosis in nonhypertensive patients with diabetic retinopathy showing venous obstruction. The correlation between the obstructed vein and arteriosclerosis of its accompanying artery was also noted. They further cited examples of this same phenomenon in other tissues of the body. They believed that retinal venous engorgement gave rise to functional arterial spasm which if sustained finally produced retinal arteriosclerosis. They believed these alterations were initiated by a vein-artery reflex of undetermined nature.

There are few pathologic reports of copper- and silver-wire arteries. Especially is this true of arteries seen clinically and consecutively studied under the microscope.

Gunn [1] originally prophesied that copper-wire arteries would show hyaline degeneration of the wall.

In 1913, Coats [10] studied microscopically 36 eyes with obstruction of the central retinal vein. In only three of these were the retinal *arteries* and veins normal. None of these cases had been studied clinically beforehand, so there could be no correlation of the clinical picture and microscopic findings. Coats described a thickening of the arterial wall due to fibrous proliferation of the wall connective tissue. He stated that the muscular layer did not take part in this process but became atrophic. The wall thickening led to a concentrically narrowed lumen. As a further step in this process, fibrous and hyaline degeneration of the thickened wall could lead to vessel closure.

Interpreting these changes, he believed that endothelial proliferation gave the irregularity of caliber without wall thickening and that the fibrous degeneration gave the increased reflex on the vessel and beside the column of blood (silver wire).

In 1916, Moore [11] described an artery seen clinically as "exceedingly bright and burnished" and he called it silver wire. I believe, in view of Ballantyne's discussion presented earlier in this paper, that it would today have been called a marked copper-wire artery. This artery microscopically showed "fibrosis of the middle coat." The illustration of it showed no narrowing of the lumen, no endothelial proliferation, and very indistinct markings of the thickened layer. Moore also strongly stressed the obstruction to vein flow in retinal arteriosclerosis.

In 1930, Friedenwald [12] described silver-wire arteries as showing hyaline degeneration of the media with narrowing of the lumen. He too stressed the importance of venous obstructive phenomena in retinal arteriosclerosis.

In 1938, Ballantyne, Michaelson, and Heggie [13] reported the microscopic findings in a 57-year-old woman with essential hypertension who had an enuric death. A retinal artery had shown pipe-stem sheathing and was studied by serial section. The

only reference to the veins indicated some venous stasis.

The central retinal artery and comparable arteries of the kidney and brain showed marked proliferation of the subendothelial cells, multiplication of the elastic fibers, irregular thickening of the intima, narrowing and eccentricity of the lumen, and, in some places, disintegration of these proliferated endothelial cells into fatty debris. The retinal arteriole with pipe-stem sheathing showed an analogous change.

They concluded that the subendothelial tissues proliferated first, causing an irregular narrowing of the lumen without clinically visible wall thickening. As these cells degenerated with fatty change, the wall became clinically opaque as pipe-stem sheathing. They pointed out that such pipe-stem sheathing due to intimal disease should not extend beyond the width of a normal blood column, as the opacity was due to a thickening into the blood column, so to speak. As they freely stated, "The investigation of this case does not prove that pipe-stem sheathing is always intimal."

One of the major characteristics of the arterial pipe-stem sheathing after vein obstruction is its extension well beyond the width of the original blood column. Thus, Ballantyne, Michaelson, and Heggie's case probably represents a different type of pipe-stem sheathing than that herein reported.

Present Study

For the past eight years a clinical study of the venous and capillary obstructive retinal diseases has been under way at New York University. However, only in the last year has special attention been paid to the secondary effect of vein obstruction on the accompanying artery. Even in a short study such as this, some findings were so obvious as to be self-evident. Others, though strongly suggested, will need further clarification.

As a working hypothesis the following concept is proposed: An arterial disease, independent of hypertension, occurring usually in persons over 60 years of age but sometimes seen in younger persons is characterized clinically by a paler color of the arteriole, a broadening of its axial light streak, and the development of a thin light streak on either side of the blood column. Such arterioles may be narrow and straight with acute branchings or more normal in contour and width. An arteriosclerotic plaque at the lamina cribrosa may well be responsible for the narrowing and straightening of such retinal arterioles as suggested by Friedenwald.[12] These changes would then be totally independent of the process under discussion.

Ballantyne[2] called this a senile change and stated that microscopically such arterioles showed endothelial proliferation and fibrosis or hyperplasia of the fibrous coat. Elwyn[14] spoke of it as aging with loss of elasticity. It has also been called involutionary sclerosis with replacement fibrosis. At any rate, this sclerosing process of the arteriolar wall may spread to the venous wall at A-V crossings or at the lamina cribrosa, where artery and vein have a common adventitia. Subsequently, increasing venous obstruction may ensue with the passage of time. Hypertension may be totally absent, but its onset speeds up this process, so to speak.

When multiple A-V crossing defects appear due to this process, widespread venous impedence and stasis result and the retina becomes hypoxic. The prolonged stimulus of this hypoxia may be a factor in arteriolar dilatation, or with the onset of hypertension a weakened wall and higher internal pressure may cause dilatation. Zweifach[15] has shown that local tissue stimuli may override systemic stimuli acting on the small arterioles, even when the systemic stimuli are of maximum intensity.

Therefore, coincident with increasing signs of venous obstruction, arterioles especially of the first, second, and third order become sinusoidal and dilated, have a more brilliant reflex, and are called copper wire. Careful slit-lamp study will reveal fine irregularities and a granularity of such arteriolar wall changes. "Arteriosclerotic

plaques" may appear on such arteries in the absence of complete vein obstruction. These are yellowish white, highly reflecting thickenings of the arteriolar wall, which have a special predilection for bifurcations and to less extent for bends in the arteriole and A-V crossings. They completely or partially hide the blood column from view and at times appear to have a crystalline content. Such plaques extend beyond the edge of the blood column, appear to involve the outer arteriolar wall, do not usually interfere with the vessel patency, and may disappear in time without residual evidence of their presence.

When the central retinal vein or one of its branches becomes completely obstructed, the accompanying arterioles lie in a much more stagnant and hypoxic field. Characteristic though variable changes in the arteriole usually follow. I have seen minor degrees of this as early as three months after the vein obstruction, and one of the most full-blown pictures developed in nine months. The arteriolar changes probably depend to some extent on the condition of the vessel before the obstructive episode.

Some arteriosclerotic arterioles are narrow and straight with angular twists, others are more dilated and sinusoidal with gentle curves, and sometimes short segments show very minute and bizarre twisting. The blood column may be invisible, visible as a thin thread, or patchily visible as a very irregular column wider here and narrower there. The arteriosclerotic wall occasionally appears as a dirty gray smoother streak but characteristically is a yellow-white color, dense and coarsely granular in character, and sometimes it contains crystalline areas. Some arteriosclerotic arteries could be likened to a salted pretzel, while a more typical appearance would be that of a ragged suit on a scarecrow. At the ragged ends of a pipe-stem sclerosis there is often a clear zone between the normal edge of the blood column and the terminal sclerosis of the outer arterial wall, suggesting that the process begins in the outermost layers of the arteriolar wall (Figs. 1 and 2).

If an arteriole passes beyond the area of vein obstruction, it loses its pipe-stem coat and becomes more normal in appearance. In a retina with considerable venous stasis arterioles may appear copper wire, except in the area of complete venous obstruction where typical silver-wire change is apparent. Also, arterioles passing through circinate areas of retinal hypoxia[8,16] sometimes show smaller degrees of this same secondary sclerosis in that portion of the vessel lying within the ring lesion (Fig. 3). For these reasons, it seems apparent that the major arteriolar change is due to the effect of some noxious agent in the stagnant zone acting on the wall from without.

Some spots of typical silver-wire pipestem sheathing, if removed and placed on the bifurcation of a copper-wire artery, would have the exact appearance of a so-called "arteriosclerotic plaque."

Most of the arteries showing secondary arteriosclerosis in this series have been shown to be patent by field examination. I would, however, anticipate that many of these would eventually close if followed for a sufficient time.

Finally, it appears that if good collateral venous circulation is established secondary arteriosclerosis is less likely to develop. Four typical cases follow.

Report of Cases

CASE 1.—A 65-year-old man, mildly diabetic but without diabetic retinopathy and without hypertensive cardiovascular disease (B. P. 142/85), was observed by Dr. Robert Coles, during which time he developed an obstruction of a right superior temporal vein branch at an A-V crossing and of the left superior temporal vein at an A-V crossing. All of the changes typical of a previous vein obstruction—aneurysms, neovascularization, hemorrhages, collaterals, edema, and one patch of fibrosis—were present in the obstructed area O. S. The superior temporal artery in this zone showed a marked moth-eaten arteriosclerosis. A thin thread of blood could be seen through the sclerosed artery. Elsewhere in

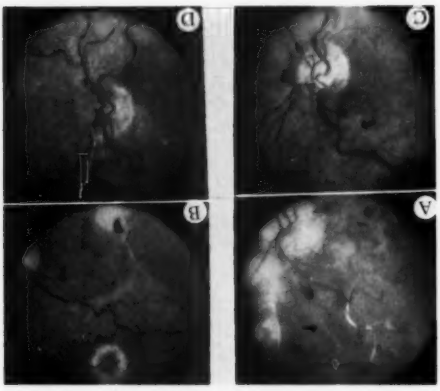


Fig. 1.—*A*, a 65-year-old woman with severe hypertensive retinopathy, B. P. 250/130. Old obstruction of right superior temporal vein (see arrow). Secondary sclerosis of accompanying artery. *B*, a 72-year-old woman, B. P. 160/80. Obstruction of right superior temporal vein five years previously. Secondary sclerosis of accompanying artery (see arrow). *C*, a 65-year-old woman with moderate hypertension. Obstruction of right superior temporal vein Dec. 1, 1954. This photograph was taken two years later. Secondary sclerosis of accompanying artery (see arrow). *D*, a 56-year-old woman with four-year history of hypertension, B. P. 210/135. O. S. enucleated for thrombotic glaucoma. Photograph shows O. D. with incomplete or slowly developing obstruction of the central retinal vein. Collaterals on disc, but most retinal aneurysms and neovascularization in region of superior artery showing moth-eaten secondary sclerosis. Copper-wire arteries elsewhere. All cases showed typical retinal findings in area of previous vein obstruction: neovascularization, aneurysms, edema, hemorrhages, halo sheathing of vein, collaterals, etc.

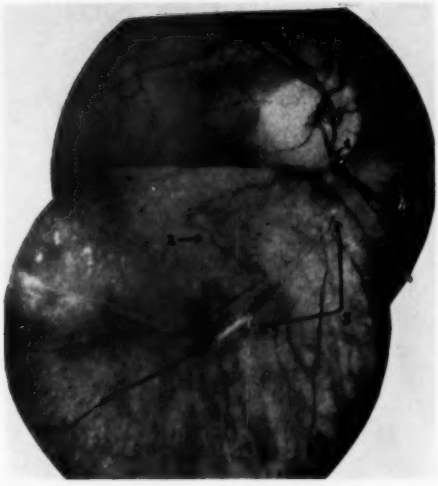


Fig. 2.—A 58-year-old woman with severe hypertension for 15 years, B. P. 240/160. First arrow shows position of original obstruction of right inferior vein at an A-V crossing six months previously. Second arrow shows venous collaterals about inferior temporal vein obstruction. Third arrow shows secondary arteriosclerotic plaque and sleeve of accompanying artery.

the fundus the veins were dark and dilated and showed faint halo sheathing, all indicative of milder stasis, and arterioles elsewhere were typically copper wire (Fig. 4).

Field examination revealed all arterioles patent (Fig. 5).

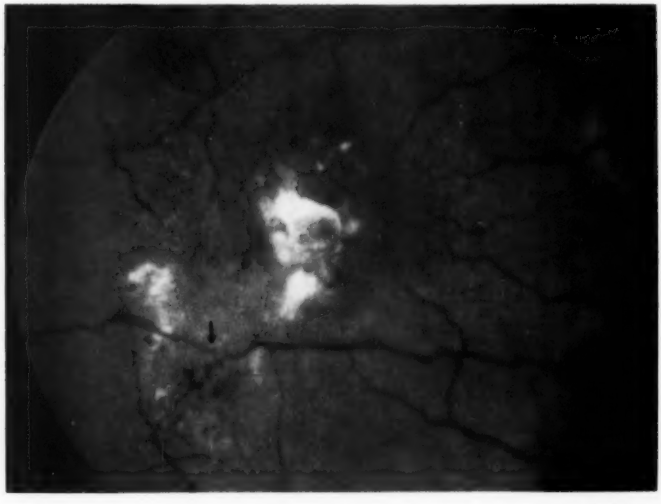
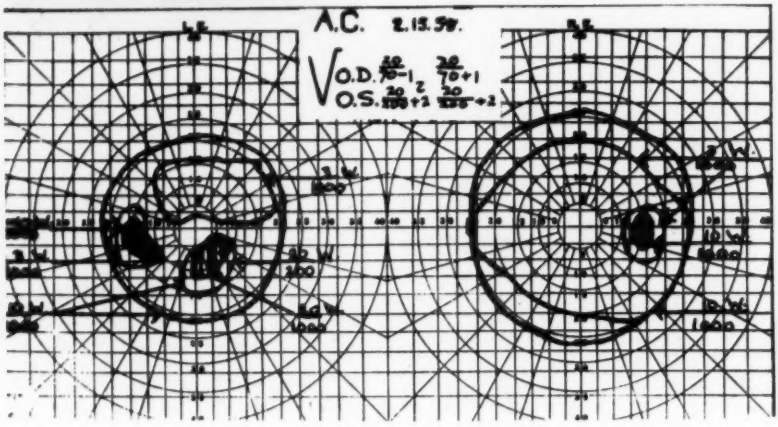


Fig. 3.—A 76-year-old woman with circinate macular lesion O. D. following slowly developing "silent" central vein obstruction. Arrow shows secondary sclerosis of the artery as it passes through this circinate area of retinal hypoxia.

Fig. 4 (Case 1).—Compare the secondary arteriosclerosis of the left superior temporal artery (arrow) accompanying the previously obstructed vein with other arteries in unobstructed areas.



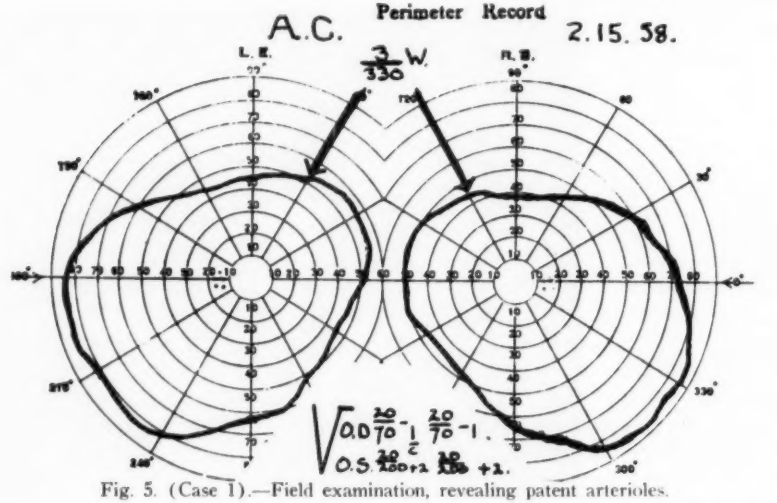


Fig. 5. (Case 1).—Field examination, revealing patent arterioles.

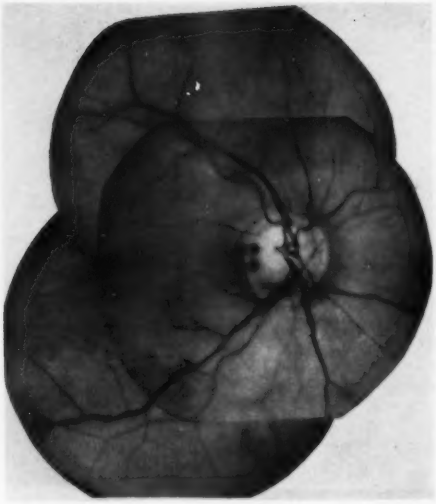


Fig. 6 (Case 2).—O. D. showing mild arterial narrowing with increased light reflex. Compare with artery in obstructed venous area in Figure 7.

Fig. 7 (Case 2).—O. S., obstruction of the superior temporal vein with secondary arteriosclerosis of the accompanying artery (arrow). Photograph is slightly rotated to left.

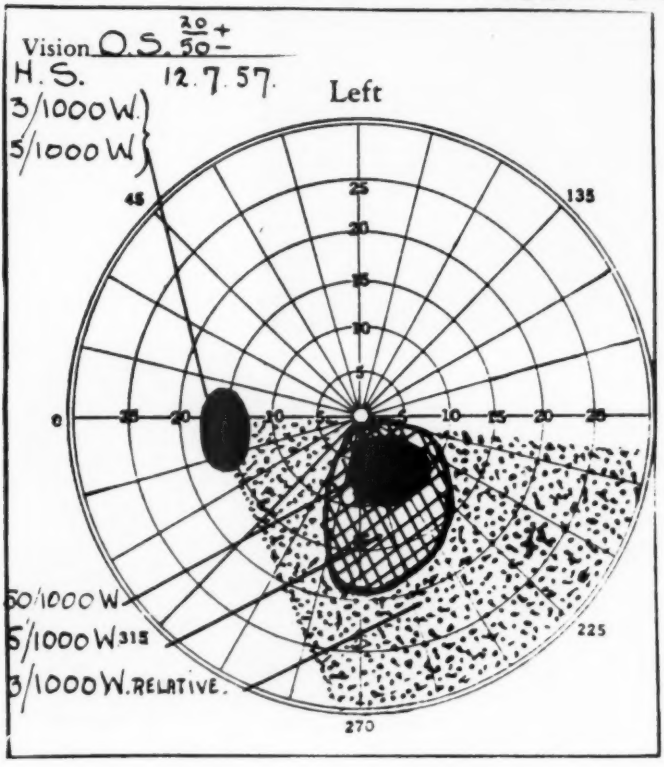


Fig. 8 (Case 2).—Central field examination indicative of venous rather than arterial obstruction.

Fig. 9 (Case 3).—O. S. showing minimal arteriolar narrowing and increased light reflex.

Fig. 10 (Case 3).—O. D. showing classic obstruction of central retinal vein of four days duration.

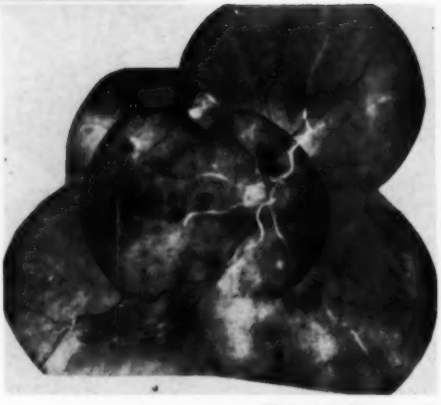


Fig. 11 (Case 3).—O. D. showing appearance nine months later—classic secondary arteriosclerosis.

CASE 2.—A 56-year-old woman with known hypertension for 10 years (B. P. 150-180/100-110) had been seen at intervals by Dr. Gerard DeVoe since 1952. She had regularly shown spastic arteriolar narrowing with increased arterial light reflex but only once showed two cotton-wool exudates, which subsequently disappeared. On April 10, 1953, she was diagnosed by Dr. DeVoe as having an obstruction of the left superior temporal vein at an A-V crossing on the disc. The fundus was typical. Her picture slowly evolved through the ensuing years until November, 1957, when I examined her.

At this examination, the corrected vision was normal in each eye. The fundus findings were as follows:

O. D.: The smaller arterioles were narrow with fine irregularities and acute branchings. The larger arterioles were pale and sinusoidal and showed increased light reflex. There were A-V defects, and the veins beyond some of these were full. There were no hemorrhages or exudates (Fig. 6).

O. S.: The disc was pale in the upper temporal quadrant. The superior temporal vein was obstructed from a point deep in the physiological cup. There were venous irregularities peripheral to the obstruction as well as edema, neovascularization, aneurysms, and a few collaterals to both adjacent patent veins. There was a brownish beaten silver appearance of the macula with a slightly disturbed foveal reflex and a mild macular edema. The accompanying arteriole showed marked secondary sclerosis completely hiding the blood column from view in places. In other quadrants the arterioles and venules were as in the other eye (Fig. 7).

The field of vision corresponding to this quadrant was depressed but not obliterated, and there was a dense subcentral paramacular scotoma, findings compatible with venous rather than arterial obstruction (Fig. 8).

CASE 3.—A 73-year-old woman had had known hypertension and mild diabetes for the preceding five years, the latter controlled by diet alone. Four months before her first eye examination she had noticed blurred vision of the right eye. Four days before I first saw her this had become much worse.

Examination on May 25, 1956, revealed the vision O. D. to be finger counting at 1 ft. O. S., 20/40. The left fundus showed minimal arteriolar narrowing and increased light reflex with a single punctate hemorrhage below the disc. There were no exudates (Fig. 9). The right fundus showed classic central retinal vein obstruction (Fig 10). On Nov. 15, 1956, the vision of the right eye had improved to 20/100 and the fundus was clear enough to see a greatly increased arterial reflex on the superior temporal and inferior nasal arteries. On Feb. 7, 1957, the fundus had cleared considerably and marked secondary arteriosclerosis of all retinal arterioles was obvious (Fig. 11).

A careful review of her fundus findings in September, 1957, showed little change and was as follows:

O. D.: Vision, 20/100. The disc was slightly pale, and on the surface were small venous collaterals. The arteries showed marked irregular pipe-stem sheathing with crystalline deposits in places. Some areas of arteriolar wall were almost free of sheathing. All signs of the previous central retinal vein obstruction were present: aneurysms, neovascularization, retinal edema, and persistent hemorrhage. The veins were irregular and showed halo sheathing. There were pigment atrophy and proliferation, neovascularization, preretinal mild fibrosis, and suggestive fine retinal folds at the macula.

O. S.: Vision, 20/40. The fundus showed a few punctate and blot hemorrhages but no exudates. The arteries showed mild increased light reflex and minimal narrowing in places.

Field examination of the left eye was normal. The right eye showed general depression in all quadrants with a paracentral scotoma. Peripheral and central fields in this eye proved arteriolar patency (Fig. 12).

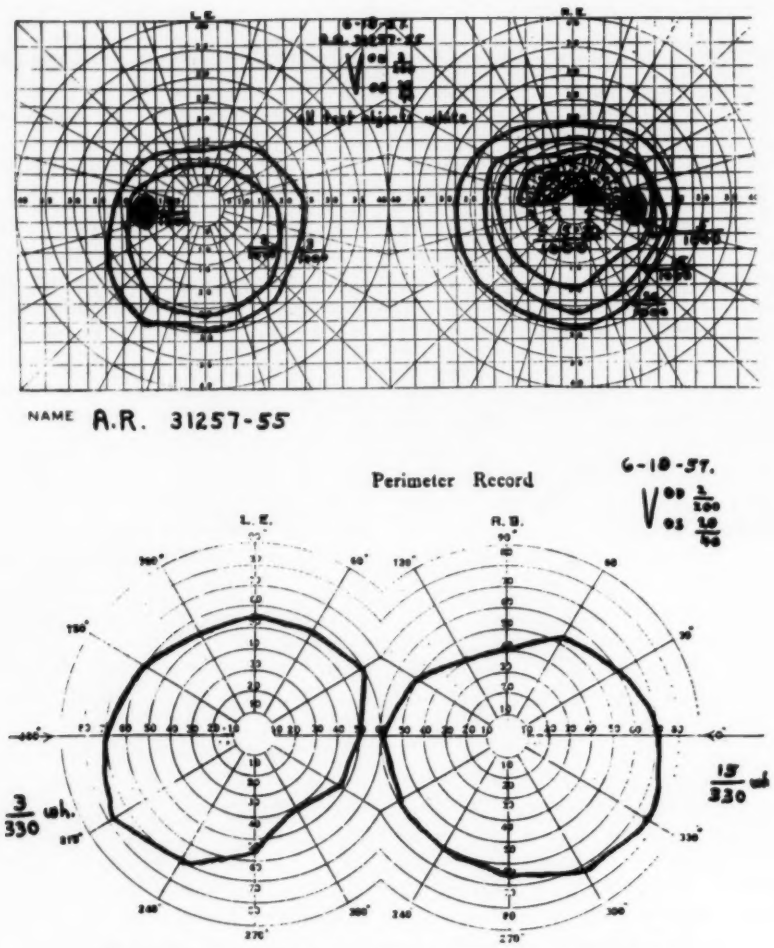


Fig. 12 (Case 3).—Field examination showing patent arterioles.

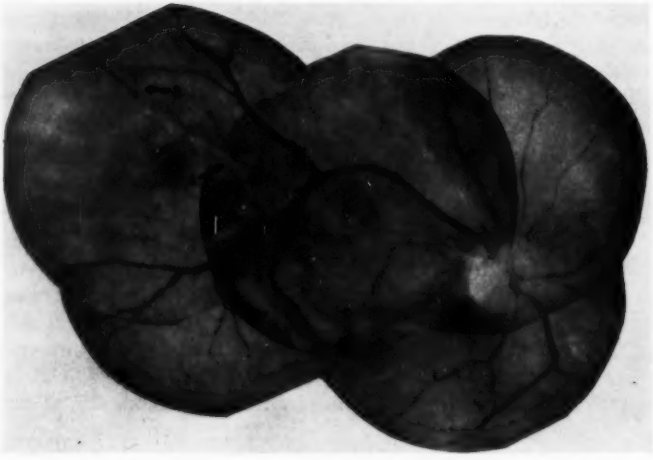


Fig. 13 (Case 4).—O. D. two years after obstruction of right superior temporal vein. Arrow (*1*) shows secondary arteriosclerosis of accompanying artery. Compare with other normal arteries. Arrow (*2*) shows shunt where sludged blood returning toward the disc in the peripheral portion of this artery connects with the superior temporal vein.

CASE 4.—A 26-year-old woman had had three miscarriages and moderately severe colitis for the three previous years. A thorough hospital evaluation was nonrevealing. Her cardiovascular system was normal, with normal blood pressure. Dr. Marvin Gillman saw her at the time of a classic obstruction of the right superior temporal vein. I first examined her on Feb. 4, 1958, two years after this episode.

Examination revealed vision O. D., $-1.00 = -0.75 \times 80$—20/20; vision O. S., -3.25 sph. 20/20.

O. S.: Completely negative.

O. D.: The superior temporal vein was dilated, dark, and beaded as it arched over the macula. The superior temporal artery from the disc to a point was narrowed and

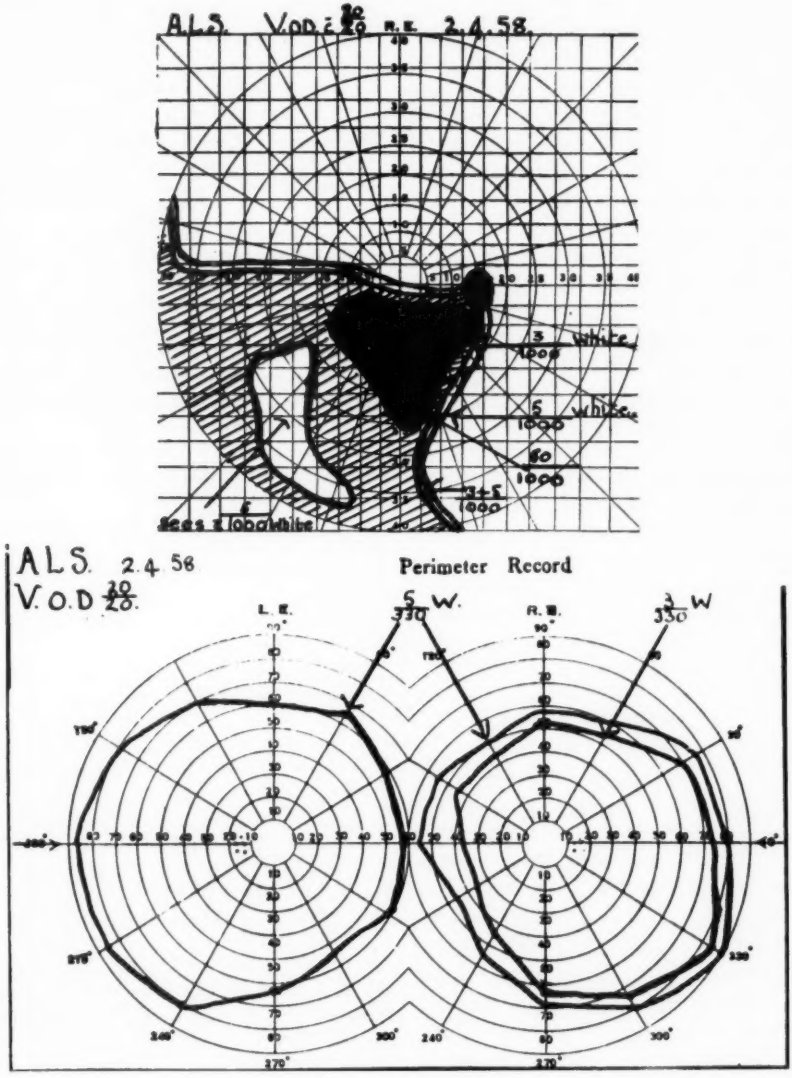


Fig. 14 (Case 4).—Field examination showing patent arterioles.

showed classic moth-eaten to heavy sleeve-like secondary sclerosis obliterating the view of the blood column in many places. At this point the sclerosis suddenly ceased, and from here outward the artery looked like a vein and carried sludged blood toward the disc. At the beginning of the sclerosed portion this sludged blood passed through a shunt to the previously obstructed and now partially functioning superior temporal vein. While this sector of the original artery, now acting as a vein and carrying sludged blood toward the disc, was being watched, two arterial branches from the sector carried sludged blood in irregular spurts or slow steady movements toward the tissue. At a later observation these small arteriolar branches were closed and another had opened to squirt sludged blood again toward the tissues. The previously closed branches were invisible, and between squirts this small arteriole could not be seen. In this general area of the fundus there was a delicate fine network of vessels containing sludged blood, some moving slowly and some seemingly stationary. No aneurysms or halo sheathing of veins was noted. A smaller arteriole above the disc near the border of the zone of stasis showed a much smaller degree of secondary sclerosis (Fig. 13).

Field examination showed a depression of the lower nasal field and a dense paramacular scotoma below the fixation point. Arterial patency was demonstrated (Fig. 14).

Summary

Copper-wire and silver-wire or pipe-stem arteries have been considered generally as representing varying degrees of arteriolar sclerosis due directly to severe or prolonged hypertension. This idea has gained prevalence in spite of Gunn's original description of the associated venous stasis and in spite of the few voices raised against this concept.

A silver-wire or pipe-stem secondary arteriosclerosis results from some noxious effect on the outer arteriolar wall when such an arteriole lies in the stagnant area of drainage of a previously obstructed vein or an area of severe capillary obstruction (circinate lesion). Hypertension need not be present. The prevalence of such arteriolar change in hypertensive fundi is due to the severe degree of associated venous stasis or obstruction in this disease. Evidence is presented suggesting that copper-wire arterioles and "arteriosclerotic plaques" represent a milder degree of this same phenomenon due to venous stasis rather than to complete vein obstruction.

550 1st Ave. (16).

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Hyaline Bodies of the Human Optic Nerve

Histopathologic Study of a Case of Advanced Syphilitic Optic Atrophy

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The occurrence of hyaline bodies (amyloid bodies) in the human optic nerve is rather common. It is rare, however, to observe such a tremendous number of hyaline bodies in the optic nerve as we did in the present case of optic nerve atrophy in acquired syphilis.

Report of Case

This is the case of a 54-year-old white man who died on May 1, 1958, in the Ypsilanti State Hospital, Michigan. The patient had acquired syphilis in 1927, at the age of 23. He was treated with bismuth, mercury, and arsphenamine (Salvarsan). After 11 weeks of such treatment the blood tests for syphilis were negative, and regular blood tests every 9 to 12 months for the next four years were also negative. In 1946, however, the patient was laid off as a factory worker because of failing eyesight. The plant doctor then found that his vision was 20/60 O. U. Over the next years his vision became gradually worse. In 1947, he was examined, treated, and also admitted in several hospitals of this area. Blood and spinal fluid were found to be positive for syphilis. The colloidal gold curve was that of the paralytic type. In July, 1947, the patient was treated in a Detroit hospital with malaria inoculation and with a total of 13,960,000 I. U. of penicillin. At the end of 1947, the patient attempted suicide (cutting throat with razor blade) and was transferred to Wayne County General Hospital, Eloise, Mich. The diagnosis then was (1) general paresis, (2) primary optic atrophy (syphilitic) O. U., and (3) recent lacerated wounds of the neck.

In 1950, the patient was blind in the right eye and had only light perception in the left. An eye examination at the Wayne County General Hospital in 1957 showed the following findings: There was blindness O. D. and light perception O. S. The right pupil was slightly larger than the left and showed no direct reaction to light. The left pupil reacted sluggishly to light. Both optic disks were well defined but very pale. The retinal blood vessels were small. There were Grade II arteriosclerotic vascular changes.

On May 1, 1958, the patient died in the Ypsilanti State Hospital of dissecting aneurysm of the aorta.

Histologic Method.—The intracranial and parts of the intraorbital portions of the optic nerves of this patient were removed at postmortem and fixed in bromformalin. Frozen sections of the nerves were made in longitudinal direction. These sections were stained with the methods of "double impregnation without reduction" and with the method for astroglia of del Rio Hortega as described by Scharenberg and Zeman.[1]

All illustrations presented in this paper are unretouched photomicrographs.

Histologic Findings.—Both optic nerves were atrophic and showed an extensive increase of all their connective tissue structures. The outstanding findings in both optic nerves were a very advanced degeneration of the nerve fibers (neurites) and the presence of extremely numerous round

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From the Department of Ophthalmology and the Laboratories of Neuropathology and Neuro-Ophthalmology of the University of Michigan Medical Center.

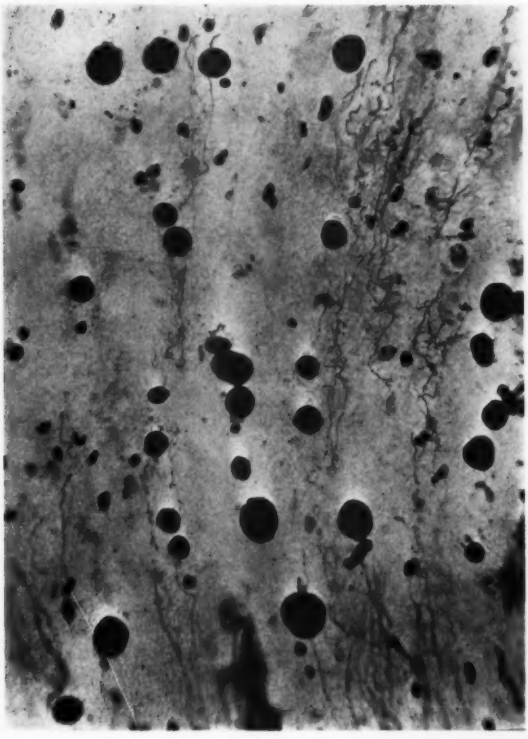


Fig. 1.—Area of a longitudinal section of the right optic nerve. There are only few atrophic nerve fibers and many hyaline bodies. Frozen section, Hortega method; × 400.

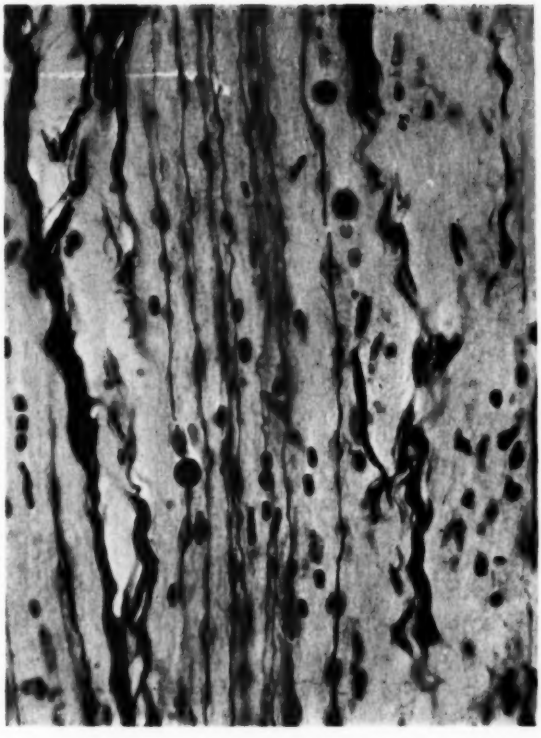


Fig. 2.—Another area of a longitudinal section of the right optic nerve which exhibits a loose bundle of surviving nerve fibers. One small hyaline body is seen within the bundle. The coarse structures represent connective tissue structures of the septae. Frozen section, Hortega method; × 400.

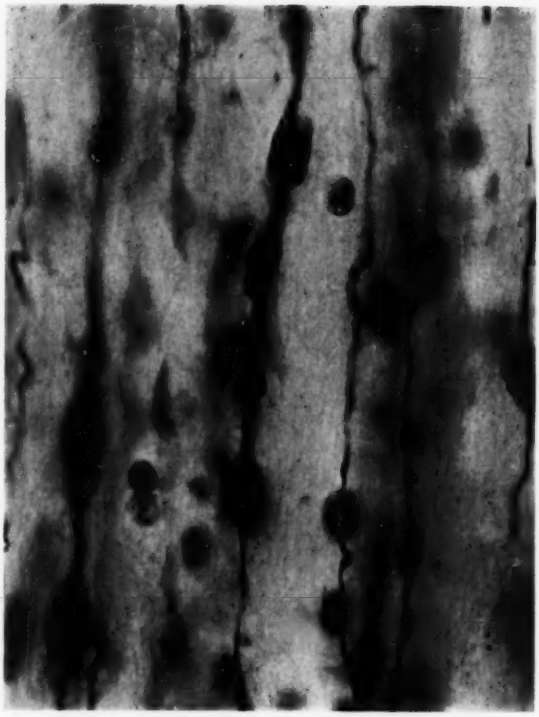


Fig. 3.—High-power view of nerve fibers of the right optic nerve which exhibit the pearl-string-like changes. The nerve fibers are continuous. The pearls are composed of local swellings of the myelin sheaths and of the swollen and tortuous neurites. The nerve fiber parts between these pearls appear about normal. Longitudinal frozen section, Hortega method; × 900.

Fig. 4.—High-power view of another nerve fiber bundle of the right optic nerve. The nerve fiber parts between the pearl-like swellings have disappeared, while the swellings (*a*) have survived. Some of the swellings (*b*) show homogenization and hyalinization. Longitudinal frozen section, Hortega method; × 900.

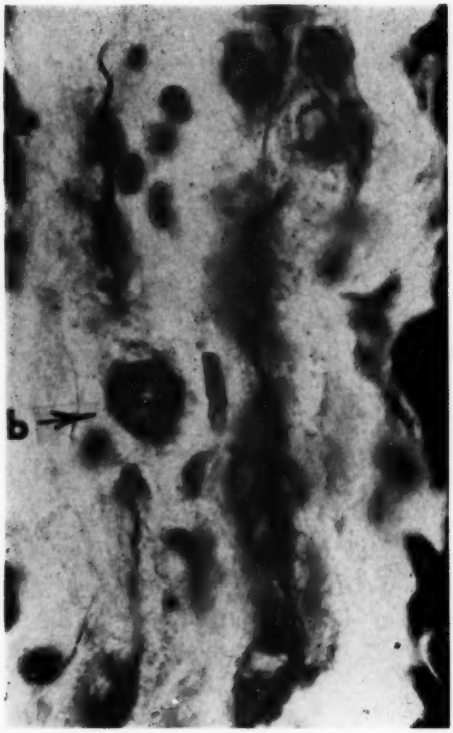


Fig. 5.—Partly disintegrated and fragmented nerve fiber which shows a pearl-like swelling with early hyalinization. Longitudinal frozen section of right optic nerve, Hortega method; × 900.

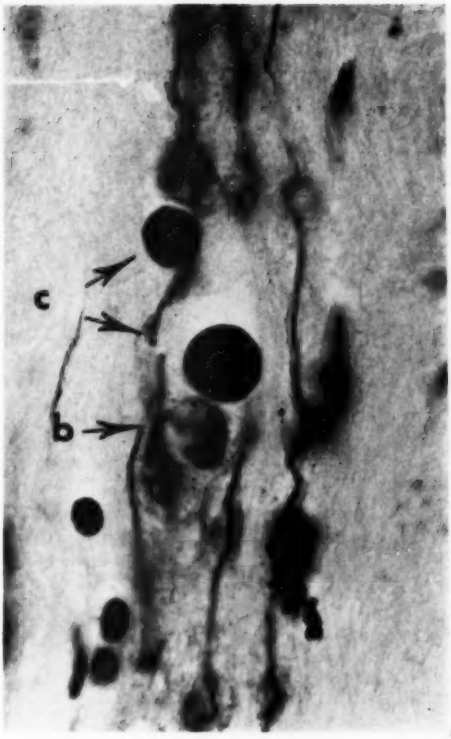


Fig. 6.—Different stages of early (*b*) and advanced (*c*) hyalinization of surviving pearl-like swellings of nerve fibers with fragmentation and partial disintegration. Longitudinal frozen section of right optic nerve, Hortega method; × 900.

Fig. 7.—High-power view of a longitudinal section of the right optic nerve. There is pearl-string-like degeneration of the nerve fibers. One large surviving pearl-like swelling still shows the neurite in it (*a*). Another swelling is completely hyalinized (*c*). Frozen section, Hortega method; × 900.

Fig. 8.—One pearl-like swelling (*a*) still in connection with the nerve fiber and two completely hyalinized ones (*c*) in the right optic nerve. Frozen longitudinal section, Hortega method; × 900.

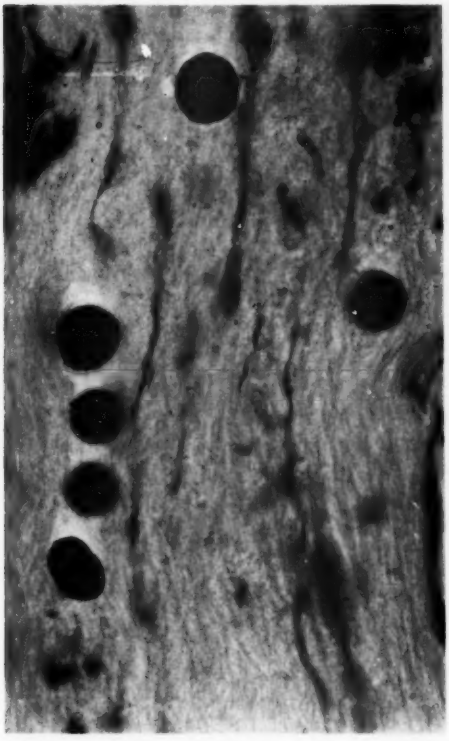
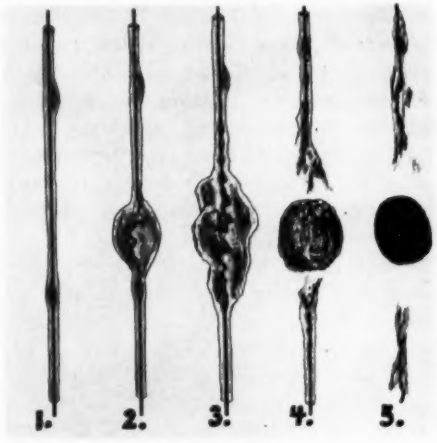


Fig. 9.—Hyaline bodies after complete disintegration of the nerve fibers. The row of hyaline bodies at the left still indicates its origin from one nerve fiber. Frozen longitudinal section of the right optic nerve, Hortega method; × 900.

hyaline (amyloid) bodies (Fig. 1). These hyaline bodies showed an irregular distribution all through the optic nerves. They were always found within the atrophic nerve bundles and showed no relations to the mesodermal structures of the optic nerve. Further studies of the histologic sections showed these hyaline bodies to be the end-result of a peculiar nerve fiber degeneration. All stages of this degeneration were seen and will be demonstrated in the following. It must be emphasized that there was no difference in the histological findings of the right optic nerve, the eye of which was blind, and the left optic nerve, the eye of which still had light perception at the time of death.

There were still some continuous nerve fibers in the atrophic bundles of both optic nerves (Fig. 2). Many of these fibers, however, showed peculiar pathologic changes. They were shaped like strings of pearls (Fig. 3). The pearl-like swellings

Fig. 10.—Development of hyaline bodies (*5*) in this case from nerve fibers of the optic nerves (*1*). The stages of this process are the formation of pearl-string-like swellings (*2*), disintegration of the nerve fiber parts between the swellings (*4*), homogenization and hyalinization of the swellings (*4* and *5*), and survival of the hyaline bodies.



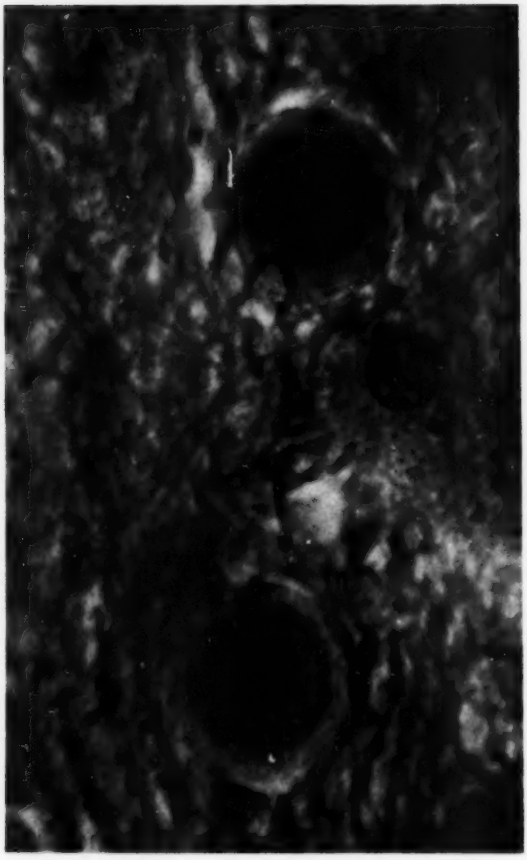


Fig. 11.—High-power view of hyaline bodies in the left optic nerve. Paraffin section, hematoxylin and eosin; × 1,000.

were composed of the myelin sheaths and the neurites. The neurites in the area of these pearls were clearly swollen and tortuous (Figs. 3, 4, and 8). The myelin sheaths and the neurites in the areas between these swellings appeared to be normal. It was obvious that these "pearl-string-like" changes of the nerve fibers represented the early phase of a degenerative process.

Other nerve fibers exhibited the same pearl-like swellings but showed also advanced changes of the nerve fiber areas between the pearls. These parts of the nerve fibers exhibited all stages of destruction and disintegration (Figs. 3 to 8).

Only the pearl-like swellings of the nerve fibers were found to have survived after the parts of the nerve fibers between them were destroyed. At the same stage these pearl-like swellings became larger and more homogeneous (Figs. 4 to 6). Parts of the tortuous neurites within the swellings were no longer visible, and there was progressive hyalinization. The end-result of this process of progressive hyalinization and homogenization were round hyaline bodies (Figs. 6 to 8). The arrangement of these bodies in rows often indicated their origin from nerve fibers (Fig. 9).

The drawing (Fig. 10) demonstrates the stages of the nerve fiber degeneration which resulted in the formation of hyaline bodies as observed in this case.

The conventional stains also showed the large number of hyaline bodies within the

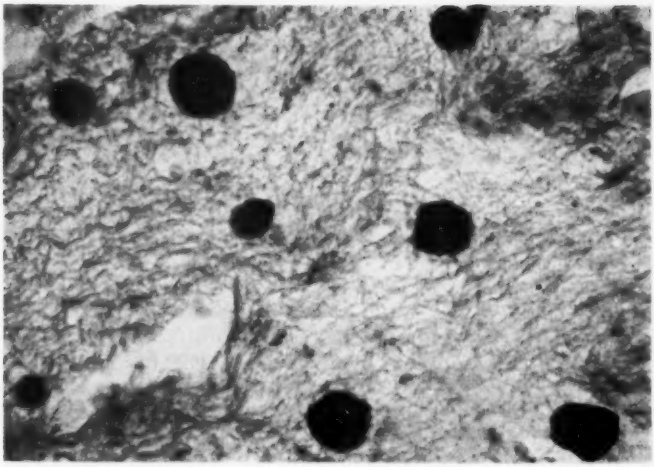


Fig. 12.—Hyaline bodies of syphilitic optic nerve atrophy; PAS stain; × 900.

nerve bundles of both optic nerves (Fig. 11). The bodies stained pink with hematoxylin and eosin. They were bright red after PAS stain (Fig. 12) and appeared light gray in sections stained with the Masson technique. A fat stain of the optic nerve sections was virtually negative.

Stains for glia revealed the astroglia to be hypertrophic. However, this hypertrophic astroglia was found in an inactive scar stage. Together with mesodermal scar tissue it had replaced the missing nerve fibers. The astroglia showed no relations to the hyaline bodies. It is of further interest that no active microglia (gitter cells) were found. This latter finding indicates that the degenerative process was extremely chronic. There was no infiltration or exudation of any kind. The optic nerve process at the time of examination was clearly that of old atrophy and slowly progressive degeneration without signs of active inflammation.

Comment

Clinically the present case represents a typical case of optic atrophy in acquired syphilis. The average interval between infection and onset of the optic atrophy is about 20 years. The interval in this case was 19 years. Optic atrophy is a typical complication of general paresis; it is commoner, however, in tabes dorsalis and taboparalysis. The pathogenesis of syphilitic optic atrophy is not completely understood. Many theories have been advanced as to its cause and nature. This, however, is not the place for a further discussion of these theories.[2]

Bruetsch[2] wrote in his book: "It is astounding that in such an important area of syphilis as represented by syphilitic optic atrophy there is still much confusion today. The main reason for this lies in the fact that histologic investigations of the various stages of syphilitic optic atrophy, which are most likely to give insight into the pathogenesis, have rarely been made." However, it seems to us that there are rather extensive studies in the literature: those of Léri,[3] Stargardt,[4] Wilbrand and Sänger,[5] Behr,[6] Richter,[7] and Igersheimer.[8] Most of these authors considered an inflammatory process the underlying cause of the syphilitic optic atrophy, which is followed by secondary degeneration of the nerve fibers. It has often been pointed out that the myelin sheaths become first involved before there is degeneration of the neurites. Only Igersheimer[8] believed that optic atrophy in some cases may be due to primary degeneration without inflammation.

The importance of this study is not that of another occurrence of optic nerve atrophy in paralytic syphilis. The importance of the present case is that it allowed for a demonstration of all the phases of a peculiar degeneration of the nerve fibers of the human optic nerve which resulted in the formation of great numbers of hyaline bodies. These hyaline bodies remained in the tissues after all the structures of the nerve fibers had disappeared. We believe that the degeneration in this case is secondary to an earlier syphilitic inflammatory process which had healed after the extensive treatment. This degeneration appeared to be nonspecific, and it is interesting that it was obviously still progressive after the inflammation had healed. It must be mentioned here that the whole central nervous system of this patient was examined histologically and that only degeneration and scarification but no infiltration were found.

Similar nerve fiber degeneration as in this present case has been seen in other cases of optic atrophy without syphilis.[9] Pearl-string-like nerve fiber degeneration of optic nerve fibers with fragmentation ("degeneration with formation of beads") has been mentioned before to occur in syphilitic optic atrophy.[2,4] The finding of such extensive hyalinization and preservation of these pearl-like swellings of nerve fibers, however, seems to be new. It is interesting that one of us found hyaline bodies in the degenerated olfactory nerve in syphilis.[10] The numerous hyaline bodies in this olfactorious were arranged identically and had developed from degenerated nerve fibers and Schwann cells.

Our interest in this case is that of ophthalmologists who want to understand and classify the possible changes which the elements of retina and optic nerve may undergo under different pathologic conditions. Hyaline bodies of the retina and the optic nerve seem to be rather nonspecific changes.[11,12] However, these durable formations represent the tombstones of certain degenerated retinal and optic nerve elements under certain conditions. They may indicate nature and phase of pathologic processes if we would learn to understand their development.

Summary

The optic nerves of a 54-year-old patient with optic nerve atrophy in acquired syphilis exhibited the late stage of a peculiar type of nerve fiber degeneration. The nerve fibers showed pearl-string-like changes. The neurites between these pearl-like swellings disintegrated, while the swellings themselves became hyalinized and remained in the tissues as round hyaline bodies.

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Annual Reviews

Diseases of the Retina and Optic Nerve

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The literature on diseases of the retina and the optic nerve continues to be extremely voluminous. Many of the articles of less importance that had appeared since publication of the last annual review [1] had to be omitted, and, of course, not all articles were found that appeared in the literature. Important papers published prior to the last annual review and located through abstract journals are included. I have reviewed only those articles I believed to be of general interest.

The art of biomicroscopy of the vitreous and of the ocular fundus is portrayed in the book by Busacca and associates.[2] Alaerts [3] preferred biomicroscopy with yellow light to visualize the capillaries and to detect pathologic changes in the retina, namely, retinal edema, exudate, and hemorrhage. The pattern of the nerve fibers is more evident in green light. Tarrant [4] described and illustrated his preferred technique for painting the retina.

Anatomy

François, Neetens, and Collette [5] demonstrated a central artery of the optic nerve, a chiasmal artery, and peripapillary retinal capillaries originating from the optic nerve vessels. They showed that the capillary network of the different parts of the optic pathway were continuous and that there was a double blood supply to the optic tract. Dejean and associates [6] showed that the central artery of the retina had no branches until it reached the lamina cribrosa. Papers by Podestà and Ullerich [7] and by Brihaye and Brihaye [8] were concerned with the same problems. Wolter [9] described small connective tissue cells, called "perivascular glia," closely surrounding the small blood vessels of the human retina. Under pathologic conditions these cells could hypertrophy and proliferate.

Development of the Retina

In the second edition of the work by Mann [10] on developmental abnormalities of the eye, she discussed the origin of congenital anomalies and the mechanism of their production for all parts of the eye, orbit, and skull. Nakayama [11] examined histologically 17 eyes from human fetuses and traced the development of the ocular tissues.

Prognostic tables of risk were presented by Cuendet [12] for sex-linked, recessive, and dominant autosomal eye diseases under various conditions of consanguinity. He made an alphabetic list of eye diseases, noted their mode of inheritance, and estimated the accuracy of genetic prognosis.

Doggart [13] stated that, except in conditions such as Tay-Sachs disease in which fundus changes are obvious, infantile fundus lesions are an unreliable guide to mental capacity because of the difficulty of distinguishing the normal from the abnormal. Valentín-Gamazo [14] and Badtke [15] reported patients with coloboma of the retina and optic nerve. Palich-Szántó [16] described a congenital anomaly consisting of a falciform fold of the retina, a retinal cyst, and a large focus that looked like a coloboma.

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Curcio and associates [17] and Emerson [18] reported on the disturbance of retinal pigment typically found in infants whose mothers had rubella during pregnancy. The latter author warned against confusing the picture of retinitis pigmentosa with that caused by maternal rubella. I concur in this warning, as patients are frequently seen who have received a diagnosis of retinitis pigmentosa with all its implications merely because of a diffuse pigment disturbance in the fundus caused by chronic uveitis, healed uveitis, maternal rubella, or other nonprogressive or treatable conditions.

Retinal Circulation

A very extensive discussion of the physiopathology of the retinal circulation was published by Bailliart.[19] Snodgrass [20] described a new graticule for measuring the width of the retinal arterioles. Lobstein [21] reviewed methods for studying the cerebral and retinal circulation and discussed measurements of pressure in the central retinal artery. Imai [22] measured the optic disc and the caliber of the fundus vessels in living animals. He then removed the eye and measured the structures directly. Hiroishi and Sugano [23] found that the corneal pulse wave arose mainly from the choroidal arteries rather than from the retinal arteries. The papers of Kittel [24] and of Kapuscinski and associates [25] were concerned with vascular pulsations in the retina. Chao and Flocks [26] injected trypan blue into the carotid arteries of cats and found the retinal circulation time to be approximately two seconds.

Bettman and Fellows [27] studied the factors that influence the blood volume of the choroid and retina. They found that only carbon dioxide systemically, certain drugs by retrobulbar injection (especially tolazoline [Priscoline] and aminophylline), paracentesis, and possibly cold to the extremities are reasonably safe and effective in increasing the intraocular blood volume. These authors and Chao [28] demonstrated by photographs of the fundus that cigarette smoking does not change the retinal vessels in most persons but occasionally constricts and rarely dilates these vessels. Dejean and associates [29] found no changes in the retinal vessels in six patients after carotid sympathectomy. Ohashi and associates [30] and Maeda [31] measured the capillary pressure in the macula under various conditions. Karsch and Gerstner [32] demonstrated an initial contraction followed by a dilatation of the vessels of the rabbit fundus when an alternating current was applied to the animal. When the current was interrupted, the vessels contracted again. They postulated that unconsciousness caused by electric injury is due not so much to anemia by contraction of the cerebral vessels as it is to anoxemia.

Zahn [33-36] measured the effect of various substances on the retinal vessels. He found that reserpine, apresoline (Hydralazine hydrochloride), pentamethonium, hydergine and phentolamine (Regitine) hydrochloride reduced the general blood pressure and the intraocular pressure but increased the retinal circulation. Procaine, tolazoline (Priscoline), nitroglycerin, and nicotinic acid reduced the blood pressure but diminished the retinal circulation. Zahn stated that dilatation of the arterioles improved the retinal circulation but drugs that dilated the capillaries and veins caused diminished circulation.

Nagase [37] found that isoniazid given orally, subconjunctivally, or retrobulbarly dilates the retinal blood vessels. Streptomycin accelerates the vasodilatory action of isoniazid while paraaminosalicylic acid decreases it. Jaeger and Seraphin [38] found that injected purified bacterial endotoxins exert a fibrinolytic and a marked vasoconstrictive effect followed by a dilatation of the retinal vessels. The pyrogenic effect is reduced by heparin.

Thuránszky and Csetri [39] produced intravascular aggregate formation in the retinal vessels by reducing the blood pressure and lowering the velocity of the blood. Apter [40] studied the isolated retina of cats and found that strychnine, mescaline, LSD (lysergic

acid diethylamide), and atropine prolonged the survival time. Pentylenetetrazol (Metrazol), ephedrine, and epinephrine had no effect. LSD produced improved vision for 48 hours in a human being with macular degeneration. Saito [41] produced only a negligible decrease in the tissue respiration of rabbit retina when the retinal artery was ligated, but a 50% decrease followed ligation of the ciliary artery. Thus, apparently the outer layer of the retina is more important in tissue respiration than the inner. Lyda, Eriksen, and Krishna [42] studied Bruch's membrane from the eye of a dog. They found that the inner third of the choroid could not be removed without tearing Bruch's membrane. Their studies indicated that molecules of the size and shape of human hemoglobin and serum albumin (molecular weight between 65,000 and 70,000) readily pass through the membrane. Molecules of γ-globulin (molecular weight of approximately 150,000) were retarded in their passage through the membrane. The isoelectric point for the membrane was found to be in the vicinity of pH 5.0.

Retinal Disease in Infants

Lemmingson and Stark [43] found that 28.2% of 301 newborn infants had retinal hemorrhages. These usually resorbed within a few days. They were not seen in children delivered by cesarean section and were commoner in first-born children. It was thought that they resulted from compression of the skull during birth. Štefek [44] examined 537 children five years after birth; 104 of these had hemorrhages into the retina immediately after birth. No changes were found ophthalmoscopically or by tests of retinal function.

Frankowska [45] studied 2,890 premature infants and found that the commonest ocular lesion was underdevelopment of the retina, mainly in the vicinity of the macula. The next commonest was retrolental fibroplasia, then refractive defects with squint, followed by nystagmus, keratomalacia with secondary glaucoma, and cataract. The majority of children with impaired eyesight were physically underdeveloped. Manschot [46] studied histologically 14 eyes with persistent hyperplastic primary vitreous and found preretinal tissue originating from retinal glial elements in 13 of them. The remaining eye had a direct continuity between the retina and the persistent hyperplastic primary vitreous.

Retrolental Fibroplasia.—Cook [47] wrote a comprehensive up-to-date review on the subject of retrolental fibroplasia. Campbell [48] reviewed the experiences of two hospitals. In one, which formerly administered large amounts of oxygen to premature infants, the incidence of retrolental fibroplasia dropped from 18.7% to 0.8% when oxygen was limited. In the other hospital, which customarily gave moderate amounts of oxygen, the incidence dropped from 7% to 0.8% when oxygen administration was curtailed. Lomíčková and associates [49] found only one child who had retrolental fibroplasia among 306 premature infants examined. A gray coloration in the thinly vascularized periphery and enlarged tortuous retinal blood vessels were frequently seen, however. Kuběna [50] reported four cases, of which two were found in full-term children. Schlitter [51] reported its occurrence in a child weighing 2,950 gm., who had never been exposed to oxygen. Karpe and associates [52] reported the experiences in Sweden with this disease.

Karvounis and Hilaris [53] found the disease in only one of twin girls who had been treated identically after birth. Babel [54] reported that in his set of premature twins only the heavier child was affected. Both had been given oxygen, but the higher concentration was administered for a short time to the affected twin because of asphyxia. Potoček [55] reported an identical situation.

Habegger and Ingalls,[56] Dejean,[57] and Véntola [58] discussed the etiology of retrolental fibroplasia. Nilausen,[59] in an interesting paper, demonstrated that the cells found at the peripheral limit of the growing vascular system in the human fetal retina are phosphatase-positive and that the entire vascularized area is phosphatase-positive, while the surrounding avascular zone is

phosphatase-negative. The enzyme was found only in the nerve fiber layer.

Crome [60] stated that retrolental fibroplasia was not always an ocular lesion primarily but could be a local manifestation of a generalized disorder. He carried out two pathologic examinations of children who died and who had retrolental fibroplasia and mental defects. One of these children was premature and had received oxygen; there was an associated patent ductus arteriosus and renal calcinosis. The second child was a full-term child, did not receive oxygen, but had the Arnold-Chiari malformation, hydrocephalus, pyelonephritis, and hydroureter. Williams [61] found a 4% to 10% incidence of mental defect in premature children, but a 10% to 40% incidence in children who have retrolental fibroplasia. Hirose and Yoshioka [62] republished their paper on the finding of this disease in three eyes of 2 fetuses among 15 stillborn anencephalics. Alfano [63] and Potoček [64] discussed the myopia of prematurity. Lomíčková [65] reported successful treatment of the incipient stages of the disease in three premature children by placing them in an oxygen atmosphere whose concentration was then slowly reduced.

Retinopathy of Diabetes

A large number of reports discussing the ocular changes of diabetes have appeared this year. Only those papers pertaining to the retina have been included in the review. Fischer [66] reviewed and discussed the first reported case of diabetic retinopathy: that of Edward von Jaeger of Vienna, in 1855. In a general review of the subject by Miratynska-Rusinowa [67] the retinal lesions were classified into three groups: (1) diabetic angiopathic retinopathy, (2) vascular diabetic retinopathy, and (3) proliferating diabetic angioretinopathy. Several excellent monographs appeared in which the entire problem of diabetes and its effect on the eyes was discussed. These include the papers by Tavares,[68] Smith,[69] Alaerts and Slosse,[70] Babel and Rilliet,[71] Constam,[72] Lister,[73] and Scott.[74]

Incidence.—Heinsius [75] found early retinal changes in 17 of 78 diabetic children. Fischer [76] found only a few cases of retinopathy in patients less than 19 years old. Dollfus and Haye [77] examined 360 diabetics less than 30 years of age and noted 22% with ocular complications. Of 100 young diabetics who had diabetes for more than 18 years, 90% had ocular lesions. Payne [78] favored the use of a free diet, as his 82 juvenile diabetics had no greater incidence of complications than was present in other series in which strict diets had been used. He found that after 20 years of the disease 64% had retinopathy, 27% had nephropathy, and 14% had hypertension, while 6 patients had died.

Fischer [79] studied 430 diabetic persons in different decades. He found that hypertension first and then arteriosclerosis were of importance in the development of retinopathy. Both nephropathy and retinitis proliferans were primarily complications of patients younger than 40 years old, while those older than 40 had arteriosclerotic changes. The same author [80] studied 54 diabetic subjects between 80 and 87 years of age and found retinopathy of diabetes present in only 10.

Janert, Mohnike, and Georgi [81] carefully studied 3,750 patients with diabetes. Of this group, 2.5% had proliferating retinopathy but generally not before the diabetes had been present 10 years. There was a close relationship between iridopathy, retinitis proliferans, and nephropathy. Kornerup [82] found retinitis proliferans in 8.4% of 1,402 diabetic patients. In most of those with severe retinopathy the diabetes developed in childhood; 28% of them were blind. He found that patients on a full diet had more frequent complications and that adrenalectomy did not retard the progress of the disease. Janert [83] also discussed retinitis proliferans.

Epstein and Zupa [84] compared 37 patients with and 37 patients without intercapillary glomerulosclerosis and found that 30 of 37 who had Kimmelstiel-Wilson disease had retinopathy while only 9 of the 37 without

Kimmelstiel-Wilson disease had retinal lesions.

Lipemia Retinalis.—Both Rouher and Contat [85] and Laws and Harpur [86] reported cases of lipemia retinalis. The latter report concerns a child 28 months old in whom the total plasma lipids measured 16 gm. per 100 ml. of serum, and most of the fat was found to be neutral fat. Cook [87] produced fatty emboli in the capillaries of the retina and kidneys of cats by giving biweekly injections of four kinds of fat. No degenerative changes were found.

Pathologic Physiology.—Ashton [88] reviewed the experimental aspects of diabetic microangiopathy and called attention to the important part played by the lipoproteins and the mucopolysaccharides, as probably both retinal and renal lesions found in diabetes are related to the increase of these substances in the blood. Alagna [89] discussed a heparin inhibition test in diabetic retinopathy. Appelmans, Doyen, and Walravens [90] reported on two patients who had acromegaly, insulin-resistant hyperglycemia, cataract, and retinal changes resembling diabetic retinopathy. Both had received x-ray treatments in early years because of severe headaches. The sella had been enlarged, but there were no field defects. One of these patients had enlarged lacrimal and salivary glands, and the other had thyroid hypertrophy with exophthalmos. Rifkin, Solomon, and Lieberman [91] could find no evidence of adrenal cortical hyperfunction in patients with uncomplicated diabetes or in patients with retinopathy or nephropathy or both.

Gerritzen and associates [92] found no retinal changes, even after 323 days, in five alloxan-treated rats that had permanent glycosuria. Cataracts developed in four of the five. No histologic changes comparable to those seen in human diabetics were found in the rats. Therefore, the authors concluded that insulin deficiency could not be held responsible for the development of late diabetic complications. Bookman and associates [93] gave 50 mg. of cyanocobalamin (vitamin B_{12}) to normal subjects, to diabetics without, and to diabetics with retinopathy and could find no significant difference between the amounts secreted in the urine of the three groups.

Forgács,[94] Nemetz,[95] Mattos and Cunha,[96] and Miratynska-Rusinowa [97] discussed the changes in the retinal vessels among diabetics with retinopathy. The last-named author found no changes in the retinal arterial pressures unless hypertension was also present. Audoueineix [98] discussed the occasional association of diabetes with cerebral edema and papilledema. Fischer [99] found changes he considered to be true diabetic choroiditis in 4 eyes out of 500 examined.

Burton, Kearns, and Rynearson [100] reported on two patients who had undergone total pancreatectomy. One had no retinal changes after 11 years, even though he had hyperlipemia and high concentration of blood sugar. The other, whose blood chemical findings were nearly normal but who had abnormal hepatic function, developed mild retinopathy three years after operation. Duncan and associates [101] reported on a patient with diabetes resulting from chronic pancreatitis and fibrosis. Diabetic retinopathy developed 24 years later and progressed to a severe degree at death.

Chalvignac [102] and Karpe, Kornerup, and Wulfing [103] found no specific changes in the electroretinogram in various types of diabetic retinopathy, except a generally low b-potential which became lower as the retinopathy became worse.

Therapy.—Neither Mylius, Stark, and Salomon [104] nor Cuendet and associates [105] expressed the belief that the diabetic hypoglycemic agents for oral use had an adverse effect on diabetic retinopathy. To treat diabetic retinopathy successfully, Brückner [106] recommended a protein-rich, fat-poor, and relatively carbohydrate-rich diet, with either insulin or sulfonyl urea and good rapport with the patient. He reported good results from the use of methylandrostenediol. Kronenberg [107] tried bishydroxycoumarin (Dicumarol), vitamin E, and lipotropic substances, such as choline and methionine,

together with flavonoids, such as hesperidin and rutin, and trypsin and testosterone but found none to be of any value in the treatment of diabetic retinopathy. On the other hand, Andreani, Fornaro, and Pagni [108] found that testosterone reduced the glycoprotein level and improved the retinopathy in four of six patients. Lindner [109] expressed the belief that rest for the eyes and the body as a whole forms an important part of the treatment of diabetic retinopathy as well as the treatment of thrombosis of the retinal vein, macular hemorrhages, hypertensive retinopathy, and chorioretinitis.

The patient reported on by Nabarro [110] experienced a definite improvement in his retinopathy following hypophysectomy. In another article, Nabarro [111] stated that adrenalectomy was disappointing as a treatment. Kurrle [112] expressed the belief that radiotherapy is of value. Paufique and Guinet [113] irradiated the pituitary.

Hypertensive Disease

A very interesting and comprehensive exposition of the subject of general vascular disease, hypertension, and arteriosclerosis was written by Leishman.[114] He divided the retinal arteriolar changes into seven categories as follows: (1) involutional sclerosis, (2) involutional sclerosis with hypertension, (3) advanced involutionary sclerosis with hypertension, (4) normal fundus, (5) early hypertension in youthful vessels, (6) fulminating hypertension, and (7) severe hypertension with reactive sclerosis. He classified the retinopathies as follows: (1) arteriosclerotic, (2) renal, (3) toxemic retinopathy of pregnancy, (4) malignant hypertension, and (5) diabetic. This article cannot be well abstracted and must be read in its entirety. A number of more or less complete articles on the general aspects of hypertensive retinal changes were published. These include the articles by Rintelen,[115] Pandit,[116] Attiah and Mortada,[117] Tadros,[118] Shelburne,[119] and Blatt.[120]

Salus [121] reviewed in an interesting paper some of the features of the retinal arterioles which may lead the observer astray in evaluating them. He called attention to the unreliability of the increased light reflex as a measure of arteriolosclerosis except in the severer grades of sclerosis, an opinion with which I concur. He used digital pressure to collapse the retinal vessels, in which case a normal reflex disappeared. Evelyn, Nicholls, and Turnbull [122] reported a detailed method of recording hypertensive changes in the retinal vessels which is suitable for experimental work but hardly for office practice.

A number of papers were concerned with ophthalmodynamometry in hypertensive patients. Bailliart [123] discussed the use of the instrument he introduced 37 years ago. He considered the finding of choked disc in the course of arterial hypertension an indication of cerebral edema. Soto [124] observed the well-known phenomenon that the retinal arterial tension is always higher proportionately to the humoral tension in hypertension than it is in normal persons. Matsui [125] reported that lowering of pressure in the retinal artery in hypertension causes increase of renal blood flow. Bonaccorsi [126] expressed the opinion that a change in elasticity of the retinal arterioles may be the first sign of alteration of the retinal walls in hypertension. Landau and Davis [127] investigated diastolic hypertension by measuring capillary pressures in the nail beds. A raised capillary pressure was not closely correlated with the blood pressure when the diastolic levels were 120 mm. of mercury or higher. Patients with proteinuria and Stages I, II, and IV of hypertensive retinopathy had high capillary pressures. Stankovic and Plavsic [128] tested the ganglion-blocking agent, pendiomide, on hypertensive patients and found no parallelism in the altered pressures in the retinal arteries and in the general arterial network after ganglion blocking. They stated that this was because the cerebral vascular system was less dependent on sympathetic stimulation than was the peripheral vascular

system. Zahn [129] carried out on his hypertensive patients a series of pharmacologic tests and evaluated them on the basis of pulse rate, intraocular pressure, systemic and retinal arterial pressure, retinal venous pressure, and the angioscotoma. This helped him to decide on the most suitable treatment for the disease.

Wolter, Phillips, and Butler [130] reported that the star figure of the macula in hypertensive retinopathy was composed of fat-filled microglia (gitter cells), of free masses of lipids, and of hyalin.

The effects of treatment were reviewed in a number of articles. These included the articles by Hick, Koik, and Johnston [131]; Healy [132]; Kincaid-Smith, McMichael, and Murphy,[133] and Barnett.[134] Filbry [135] found that more patients improved symptomatically than objectively. He postulated that improvement with regard to the angiospastic fundus changes under therapy proves that the retinal changes are not nephrogenic in origin but are probably arteriogenic hypertensive complications, linked with those of the brain and kidneys.

Fedotova [136] stated that hypertensive changes were seen in the retinal vessels of patients with coarctation of the aorta only when the coarctation was in the abdominal region. Okamune and Yamamoto [137] reported on a patient with retinal hypertensive changes who proved to have a pheochromocytoma. Etienne and Charleux [138] reported on two patients whose detached retinas reattached spontaneously after cure of their nephritis.

Toxemia of Pregnancy.—The prevention and treatment of ocular complications in the pregnant woman is the subject of an excellent article by Givner.[139] Sadowsky, Serr, and Landau [140] studied 176 cases of toxemia of pregnancy. In patients with mild (up to Group II) retinal changes, fetal mortality was 22.2%. Patients with a Group III or IV hypertensive retinopathy suffered a fetal mortality rate of 44% to 50%. Bernardczykowa and Baron [141] considered the ophthalmoscopic differentiation of the toxemias into primary and secondary forms to be most important in prognosis and treatment. Bravo and Charlín [142] reported on a large series of patients in whom they enumerated the retinal findings. Other papers were those of Freiwald,[143] Córica,[144] and Snodgrass.[145] Junceda Avelló and Junceda Avelló [146] studied the ratio of the retinal arterial pressure to the humoral arterial pressure among patients with toxemia of pregnancy and found this ratio to be increased in every instance. López Marín [147] found the ratio to be normal in pregnant women without toxemia of pregnancy. Siegert [148] reported on two patients who had bilateral detachment of the retina as a manifestation of preeclampsia. Marked pigment changes developed in the maculas of one patient. Sokolić [149] described a patient with a fundus picture which resembled that of retinitis pigmentosa and which had resulted from an attack of toxemia of pregnancy 12 years before.

Retinal Vascular Disease

The articles by Brückner [150] and Leopold [151] give an excellent review of the possible vascular disorders that cause disturbances of vision.

Retinal Arteriolosclerosis.—Rintelen [152] has expressed the view that the retinal arterioles do not present a true picture of the condition of the cerebral vessels or of the peripheral arterioles, because, he says, the retinal vessels undergo isolated senile changes at times. However, Betetto,[153] in studying histologically the artery and vein of the retina in 20 cases of disseminated arteriosclerosis and of the cerebral vessels in 15, concluded (1) that the central artery always participates in the sclerosis of the cerebral vessels but the changes in the retinal artery are usually less severe than those of the cerebral vessels, (2) that the cause of these changes is a regional difference in hemodynamic factors, and (3) that the retinal veins participate in the changes of the cerebral vessels. Sautter and Sartori [154] described pigment changes in the retina and macula, cystic degeneration, retinal detachment, and

exudative chorioretinopathy, all of which they ascribe to arteriosclerosis of the retinal or choroidal vessels. These conclusions are open to some question. De Poli, Montorsi, and Pietri [155] discovered retinal arteriolosclerosis and venous dilatation of minimal degree in 50 cases of thromboangiitis obliterans, but in 90 cases of arteriosclerosis there were periarteritis and sclerosis of both the veins and the arterioles.

Mylius and Stark [156] studied the blood fats as a factor in the pathogenesis of vascular diseases of the eye. A common feature of this type of vascular disease affecting particularly the retina and choroid was an increase in the β-lipoproteins. This was confirmed by Fischer and Kroetz.[157] Electrophoretically-determined serum lipids were increased and the macula, choroid, and other areas of the retina were affected by recent atherosclerotic changes. Treatment of the ocular changes with heparin had a beneficial effect. Voigt, Klempien, and Sartori [158] agreed.

Ophthalmodynamometry. — Weigelin [159] and Hollenhorst,[160] in brief general articles on this subject, stated that the determination of pressure in the retinal artery was of particular importance in patients who were suspected of having carotid or basilar-artery insufficiency or postural hypotension and in patients about to undergo surgical ligation of the carotid artery. Similar reports were those of Dejean, Viallefont, and Boudet [161]; Van Allen and associates,[162,163] and Rand.[164] Vanysek [165] studied the b-wave during compression of the eyeball with an ophthalmodynamometer. He discussed the results of electroretinography in high blood pressure, in arteriosclerosis, and in thrombosis of the carotid artery.

Arterial Occlusions.—Livingston [166] reviewed the etiology of amaurosis fugax and suggested that angiospasm was the commonest cause. It may follow local anesthesia near the lingual nerve in dental work, and it may be due to contrecoup injuries of the head, starvation, demyelinizing diseases, hysteria, migraine, pregnancy, tumors of the orbit or globe, cardiac disease, glaucoma, carbon monoxide poisoning, and diabetes. He recommended the use of vasodilators. Nilsson, Rendahl, and Strömberg [167] reported the very interesting case of a woman 37 years old with polycythemia vera who had a number of attacks of amaurosis fugax in the left eye. During the attacks the arterioles became very narrow, and a diagnosis of arteriospasm was made. During one attack the retina became infarcted and the vision was lost. One might surmise that the amaurosis fugax was due to retinal arteriospasm caused by an atheroma or thrombus in the ophthalmic or central retinal artery. Infarction of the retina apparently followed shortly the use of Priscoline, Papaverine, and Regitine, as might be anticipated were the arteriospasm due to partial occlusion of the vessels. Anticoagulant therapy would seem to have been indicated in this situation.

Sautter [168] called attention to the diagnosis by von Graefe in 1858 of "Embolie der Zentralarterie der Netzhaut" and stated that today it is known that this picture is nearly always caused by spasm of the retinal artery. The prognosis is said not to be hopeless even when treatment is initiated after days or weeks. Witmer and Schmid [169] observed an embolus that moved within but did not occlude the retinal artery. Lijó-Pavía [170] outlined a number of factors sometimes associated with occlusion of the central artery: diabetes, embolism, ischemic optic neuritis of temporal arteritis, spasm, aging, hypotension in the central retinal artery, the decompensated parietal tonus described by Bailliart and generally overlooked, and the endocrine humoral factor. Dejean, Viallefont, and Boudet [171] presented two interesting cases. In one, thrombosis of the retinal artery was said to be secondary to malignant change in a pituitary adenoma, while in the other, the thrombosis apparently was associated with lowering of pressure in the retinal artery that occurred some days before the actual thrombosis developed. A similar case was reported by Cossa, Duplay, and Coromine.[172]

Cordier and Saur [173] observed a spasm of the retinal artery. Mosci [174] reported occlusion of the central retinal artery in a lead worker. Sokolić [175] described a 10-year-old boy who suddenly lost vision in both eyes because of occlusions of the central arteries. Etiologically, two factors were considered to be operative: first, an inherited tendency to angiospasm, and second, an acquired sensitivity caused by infestation with Trichocephalus dispar. Blatt and associates [176] discussed the factors that produced infarction of the retina. Sartori [177] stated that most patients who suffer from occlusion of the retinal vessels show chemical changes in the blood similar to those found in arteriosclerosis, namely, increase of cholesterol and other lipids and decrease of the proteins with small molecules. Cordes [178] presented five patients in whom retinal ischemia caused visual loss. The fifth patient followed suffocation anoxia with apparently both retinal and cerebral ischemia. The second, third, and fourth patients lost vision after repeated severe hemorrhages from the stomach, uterus, and duodenum, respectively. The first patient, a very interesting one, apparently lost vision in the left eye during circulatory collapse in the course of cesarean section and had the retinal findings of central-artery occlusion. Several months later the pigment layer and the macula were found to have clumping of retinal pigment. This finding suggests that not only the retinal but also the choroidal circulation had been compromised. These are the findings reported by me [179] in the fundi of monkeys and human beings after pressure on the globe during anesthesia, and this is suggested as a possible cause.

Winter [180] reported a very interesting pathologic study of a patient who had thrombosis of the central retinal artery followed by severe secondary glaucoma. The central vein was patent. Wolter and Liddicoat [181] reported the histopathologic examination of two eyes removed because of secondary glaucoma following occlusion of the central retinal artery. Both eyes had a dissecting aneurysm of the central artery. Wagener [182] reviewed the literature on pulseless (Takayasu's) disease. This review should be read in its entirety.

Obstruction of the Central Retinal Vein. Several unusual causes of occlusion of the central vein are reported. Dorello [183] found frequent myocardial lesions among 40 patients who had retinal venous thrombosis. Catros and associates [184] reported thrombosis of the central vein following ligation of the internal carotid artery; Stephens and Welch,[185] after evacuation of a subdural abscess; Zarrabi,[186] accompanying cerebral sinus thrombosis after pregnancy, and Landau,[187] as a result of lead poisoning.

Dobree [188] mentioned two types of vascular lesions found at the optic disc in glaucoma. The first is venous thrombosis, and the second is the formation of new blood vessels. Of 200 eyes from 108 cases of chronic glaucoma, 5.5% had venous thrombosis and 10% had either coiled vessels at the optic disc or dilated capillaries. These vascular lesions were almost twice as common in the open-angle cases as they were in the closed-angle cases. Landolt [189] reported six cases of chronic simple or chronic congestive glaucoma complicated by an attack of acute glaucoma with hemorrhagic occlusion of the central vein, blindness, and enucleation.

Vannas and Orma [190] reported on 96 cases of retinal-vein thrombosis. Sixty-five per cent of these patients had generalized arteriosclerosis with or without hypertension; 73% had retinal arteriolar sclerosis; 69% had mild, moderate, or severe hypertension; 21% had an inflammatory factor present, usually sinusitis, and 10% had simple glaucoma. They concluded that anticoagulant therapy was definitely of benefit in such cases. In another article [191] these authors gave a more detailed account and it should be noted in the case reports that the control patients by and large were patients who had gone with no treatment usually from several weeks up to several months, while the treated group usually received

therapy within hours after the occlusion occurred. This might indicate that early treatment is more effective, but it more probably indicates that the patients whose results were good without treatment never reported for treatment. Mylius and Witt [192] treated 75 patients who had thrombosis of the central vein, 47 of whom had involvement of the main branch. They reported unusually good improvement in the vision under treatment with thrombocid, a synthetic drug closely related to heparin. In five cases the central vision deteriorated during treatment. Vena [193] reported on two patients treated successfully: one with heparin alone and the other with x-ray irradiation and with heparin and procaine hydrochloride given intravenously. Law [194] treated with anticoagulants only the threatened or partial occlusions but expressed disappointment with the results. Gittler [195] reported on 11 patients treated with anticoagulants, the results being similar to those in 61 patients kept under the usual treatment.

Miscellaneous.—Brini [196] discussed the vascular changes of Coats' disease. Houston and Wise [197] described the ophthalmoscopic and pathologic characteristics of various so-called circinate lesions found in venous obstruction, diabetic retinopathy, Coats' disease, Leber's multiple miliary aneurysms with retinal degeneration, and senile macular disciform degeneration. The lesion causing the circinate arrangement of waxy or hard exudates is usually a microaneurysm of the capillary system, and more rarely an arterial aneurysm, or else serous or hemorrhagic extravasation into the retinal or subretinal tissue. Ullerich and Podestà [198] postulated that stasis in the blood vessels is due to coagulation of the red blood corpuscles, while the plasma escapes into the tissues. Peters and Seitz [199] examined histologically two eyes with perivascular sheathing. One patient had chronic papilledema and the sheathing around the veins was due to opening of the intra-adventitial spaces which contained numerous leukocytes. The other patient had severe hypertension and had periarterial sheathing due to opening of the intra-adventitial spaces which were filled with protein-rich fluid.

Both Mietke [200] and Chams and Sadoughi [201] reported the ocular findings in patients who had suffered nonfatal strangulation. There were retinal bleeding, exophthalmos, spastic arterioles, dilated veins, and edema of the retina. Huerkamp [202] reported that after surgical treatment for congenital cyanotic heart disease in 42 patients the width of the retinal arterioles and the tortuosity of the vessels were not much reduced, even though the cyanotic symptoms were lessened. Ralph [203] discussed the use of citrus bioflavonoids in 89 cases of ophthalmic disorders wherein capillary fragility was a factor. The drug appeared to help in the absorption of retinal hemorrhages.

Collagen Diseases

As pointed out by Danis,[204] a large number of diseases have been classified under the heading of "collagen disease." The participation of the ocular structures is manifested in different ways: (1) by involvement of orbital or ocular collagen, (2) by primary involvement of the ocular or orbital vessels, (3) by involvement secondary to that of another organ, and (4) by toxic phenomena. Royer and Bonamour,[205] Paufique and Royer,[206] and Calmettes, Déodati, and Amalric [207] discussed the so-called dysoric retinopathy observed in lupus erythematosus as a manifestation of various of the collagen diseases. Macrae, O'Reilly, and Keville [208] discussed the neuro-ophthalmologic symptoms and signs of systemic lupus erythematosus, periarteritis nodosa, scleroderma, and dermatomyositis.

Lupus Erythematosus Disseminatus.—Hartmann and Massin,[209] Carra and Mangano,[210] and Hotz [211] reported toxic retinopathy with hemorrhages and cotton-wool patches among patients with lupus erythematosus disseminatus.

Temporal Arteritis.—There was an unusually large number of reports about patients with temporal arteritis. Palm [212] reported on 31 patients with severe visual loss, of whom the majority had ischemic papilledema, 4 had embolism of the retinal vessels, and 6 had both embolism and papilledema. Two patients apparently had intracranial involvement. The second eye was damaged in only 1 of 8 patients treated with cortisone, whereas it was affected in 15 of 17 not treated. The high sedimentation rate was stressed. Lavy and Liban [213] reported on an unusual patient who had the characteristic pathologic changes in the right temporal artery but who had an elevated level of serum globulin and an abnormal electroencephalogram, hepatosplenomegaly, and hemiplegia and who subsequently died. This patient was similar to one reported by Wagener and Hollenhorst [214] among 122 patients with the disease, of whom 54 had some degree of impairment of vision. Fifteen of the fifty-four were blind in both eyes and eighteen were blind in one eye. The commonest local cause was acute ischemia of the optic nerve. Other ocular manifestations were ischemic retinopathy, ischemic infarction of the retina, and ischemia of the extraocular muscles.

Diagnosis in most cases could be made from the history, from palpation of the temporal and occipital arteries, and by the finding of a markedly accelerated erythrocytic sedimentation rate. Occasional biopsy of the apparently involved artery was necessary. Early diagnosis and treatment with adrenal corticosteroids reduce the incidence of blindness; the simultaneous use of anticoagulant therapy is probably of help. In Rodenhäuser's [215] patient, red spots developed in the area of the skin supplied by the temporal and maxillary arteries. Histologic study showed perivascular infiltration of the precapillaries and extensive capillary ectasia. Benedict and associates [216] reviewed the manifestations of the disease. Seitz,[217] Piper and Unger,[218] Baron,[219] Nano,[220] and Meyerratken [221] all reported cases of the disease. Witmer and Schmid [222] had a patient who sustained a severe loss of vision in her only eye, and by intensive treatment with retrobulbar acetylcholine, intravenous heparin, Roniacol, and Becozym, along with Strophosid, Romicil, Ultracorten, and Tromexan, the vision returned to 20/20 in a few days.

Periarteritis Nodosa.—Otto [223] stated that ocular symptoms occur in from 10% to 23% of cases. Royer and associates [224] called attention to the numerous white spots in the retina about the vessels and the hypertensive changes, while Sheehan and associates [225] reported direct involvement of a retinal vessel by this disease, a very rare occurrence.

Purtscher's Retinopathy

Landolt's [226] patient died of massive cerebral fat embolism after multiple fractures and had typical Purtscher's traumatic angiopathy in the retina. The pathologic examination revealed fat emboli also in the uveal, scleral, and optic-nerve vessels. Diacicov,[227] Worsøe-Petersen,[228] and Braun [229] reported cases following fractures of the extremities or of the ribs. Oksala [230] found Purtscher's retinopathy following severe compression of the thorax in which there were no fractures. The retinopathy was in one eye, and a total retinal detachment was in the other. Cashell [231] reported on a patient who had retinal edema, hemorrhages, and exudation following traumatic rupture of the liver. Later these ocular lesions healed, leaving pallor of the discs, macular scarring, and diminished central vision. The retinopathy was unlike Purtscher's traumatic retinopathy due to fat emboli, but the nature of these lesions was not determined.

Coats' and Eales' Disease

Wise [232] interestingly discussed the pathogenesis of Leber's exudative retinitis, Leber's multiple miliary aneurysms, Reese's massive retinal fibrosis, and Coats' disease. He postulated that all of these have to do variously with hypoxia of the retinal tis-

sues, so that whatever vasoproliferation occurs is due to low oxygen tension. Sugar [233] described 11 cases of Coats' disease and showed photographs. He considered the retinal lesions to be the result of a vascular "leak" in eyes with telangiectasia, miliary aneurysms, or other deep vascular lesions and not a specific entity. Meyer-Schwickerath [234] reported the successful treatment of the following diseases with light coagulation: retinitis proliferans, retinal angiomatosis, Coats' retinitis, melanotic tumors, carcinomatous secondary tumors, and glioma.

Recurrent vitreous hemorrhage, or so-called Eales' disease, is reviewed completely by Wagener.[235] In some cases it appears to be due to tuberculosis. In others, of course, it is due to diabetes and sickle-cell disease. The latter two types are discussed elsewhere in this paper. Boyer and associates [236] injected radiochromium-tagged erythrocytes into the vitreous of rabbits and concluded that a diffusion process from the vitreous into the surrounding tissues and blood vessels determines the rate of removal. The same authors [237] studied the effects of enzymes, surface-active agents, and urea on radioactively tagged vitreous hemorrhages in rabbits. Enzymes and surface-active agents caused ocular damage but did not affect absorption of the blood. Urea caused damage to the vitreous and retina but accelerated absorption of the blood. Lewis [238] reported a significant reduction in intraocular bleeding time in rabbits when Premarin was used intravenously.

Bouzas [239] published data on three patients who apparently had both Eales' disease and Behçet's disease, and commented on their possible relationship. Romagnoli [240] reviewed the literature and reported clinical and therapeutic considerations in 15 cases. Gupta [241] reported on 33 patients with Eales' disease, of whom 6 showed evidence of iridocyclitis and 2 had tuberculosis. Alajmo and Simonelli [242] and Fanta [243] urged the use of diathermy as a treatment, while Anjou and Cederquist [244] condemned the use of roentgen therapy, as it seemed to be of little avail in their cases.

Kunkel [245] reported endangiitis obliterans in five patients, with retinal hemorrhages in only two. Beyer [246] reported tortuosity of the small retinal arterioles with bleeding into the macula in a 47-year-old man and his 17-year-old son.

Toxoplasmosis and Other Parasitic Diseases

Toxoplasmosis.—Three excellent summaries of the entire subject of ocular toxoplasmosis have appeared since the last review. These are by Hogan,[247] Frenkel and Jacobs,[248] and Wright.[249] Arribas and Schlaegel [250] inoculated rabbits experimentally with Toxoplasma by intraocular injection. Single cases or small series of cases were reported by Hervouet [251]; Dolcet-Buxeres [252]; Rodríguez [253]; Rawal, Patel, and Jhala,[254] and Remky and associates.[255]

Hogan and associates [256] discussed 31 cases of congenital toxoplasmosis in the newborn, in which 13 patients had a relapse either in early childhood or in adult life. In another paper, Hogan and associates [257] reported the recovery of Toxoplasma organisms from the enucleated eye of a 20-year-old man. Fair [258] reported on 8 more or less typical cases of congenital toxoplasmosis and on 21 others in which chorioretinitis was believed to be the only manifestation of the disease. He suggested that the purely ocular form might be the commonest variety of congenital toxoplasmosis and that some instances thought to be acquired might actually be congenital. Kubaštová and Jírovec [259] studied the toxoplasmin intradermal test and showed that the incidence of positive titers among patients with chorioretinitis was four times higher than the incidence in the normal population of the same age group. A similar study with similar results was reported by Perkins and Beverley.[260]

Onchocerciasis.—Several excellent papers on the ocular manifestations of onchocerciasis were published by Rodger.[261-263] He described two types of posterior degenera-

tive lesions caused by this organism: (1) an inflammatory lesion in or adjacent to the choroid, due to death of the microfilariae, and (2) a degenerative lesion associated with a low degree of infection in the individual and a low nodule number. Low values for vitamin A were found in his patients' sera. Treatment with vitamin A caused a recovery of vision in seven of the 10 patients who had the degenerative lesion. Other papers on this subject include those of Lagraulet and associates,[264] Vellieux and associates,[265] Toulant,[266] and Favory and Lagraulet.[267]

Miron and associates [268] and Goerger [269] removed intraocular Cysticercus surgically with good results. Van Buren [270] reported on a patient with blood-stream sepsis in whom, a month before death, a retinal lesion of the Roth-spot type developed, which later on section showed yeast elements in an abscess of the nerve-fiber layer. The organism was Candida albicans. Krümmel [271] described his findings in three patients in whom histologic examination of an eye showed accumulations of bodies generally lying free in the tissue spaces. In the adults, they were mostly in the episclera and the retrobulbar regions, and in the baby, in the optic-nerve sheaths. These trophozoites were 20μ to 70μ in diameter. They were identified and provisionally called Entamoeba ocularis. Galvez Montes [272] reported on two patients, of whom one had retinal periphlebitis with recurrent vitreous hemorrhages and the other had chorioretinitis, both due to ascarides. Antiparasitic treatment arrested the disease process in both cases.

Disturbances of Metabolism of Fat

Thomas and Smith [273] reported on a patient who had idiopathic hyperlipemia; and edema and hemorrhages in the retina, along with scattered yellowish areas deep in the retina which were probably multiple xanthomas. Anderson and associates,[274] in a very interesting paper, discussed the ocular lesions related to disturbances of fat metabolism. These lesions include xanthelasma, xanthomatosis of the orbit, histiocytosis (including eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease, and nevoxantho-endothelioma), arcus senilis and arcus lipidis, diffuse lipodystrophy of the cornea, lipochondrodystrophy (Hurler's), lipemia retinalis, and Tay-Sachs, Niemann-Pick, and Spielmeyer-Vogt diseases.

Kozinn and associates [275] stated that in 12 years there were 58 deaths from infantile amaurotic family idiocy (Tay-Sachs disease) in New York City. New cases number 1 in 8,300 births for Jews and 1 in 450,000 for non-Jews. A mother who has a child with the disease has a 25% chance that each subsequent child will have the disease. One in 50 Jews and one in 300 non-Jews carry the recessive gene. The disease is 10 times as common among the Askenazi Jews (who come from Eastern and Central Europe) as among the Sefardi Jews (who come from the Mediterranean area). Danis, Bégaux, and Decock [276] suggested that histologically there are two types of the disease: one type is characterized by degeneration of the ganglion cells of the retina, giving the classic cherry-red spot, and the other by disintegration of the neuroepithelium with a concomitant reaction of the pigment epithelium, giving the classic juvenile fundus lesion. They suggested that ophthalmoscopically there are four manifestations: (1) a cherry-red spot at the macula, (2) pigmentary changes of the fundus, (3) isolated optic atrophy, and (4) a normal fundus. Within any particular family only one type is seen, although the age of onset may vary. Andreani [277] reported a case of Tay-Sachs disease with bilateral optic atrophy and no macular changes. Esente and associates [278] reported the case of a female of non-Jewish descent. Svennerholm and Zettergren [279] and Gartner and Bronstein [280] reported cases of the disease. Marchand and associates [281] described the disease without amaurosis in two brothers. Gerhard [282] discussed the histologic findings in the brains of six patients. Aronson and associates [283] reported on 50 patients and

on 20 necropsies. They said that they were able to continue life beyond the average 27 months to an upper limit, so far, of 55 months. In these children who survived beyond the usual time, the cerebral hemispheres became extremely large because of glial hyperplasia. Jefferson and Rutter [284] presented two siblings who had evidence of lipid disturbance in long bones and the spinal column, Cushing's syndrome, increase of γ-globulin in the serum, and total blindness due to optic atrophy and fundus pigmentation, but with normal maculas. These were cases of the juvenile form of amaurotic family idiocy.

Blood Dyscrasias

Bosso [285] reported the pathologic study of a case of leukemia in which there was an interstitial optic neuritis with central hemorrhage and extravasation of leukemic cells surrounding a mass of erythrocytes in the retina.

Sickle-Cell Disease.—Goodman and associates [286] described five patients. There was evidence of vascular stasis and obstruction in both the retinal arterioles and the retinal venules, producing ophthalmoscopically visible retinitis proliferans, aneurysmal vascular dilatations, arborizing vascular networks, focal constrictions, sheathing and obstruction of the arterioles and venules, and retinal, preretinal, and vitreous hemorrhages. The authors point out that all patients with so-called Eales' disease should be investigated for sickling of the erythrocytes. Isbey and associates [287] reported on seven such patients. Boggess [288] and Lieb [289] wrote papers on the same subject.

Disturbances of Serum Globulins. Dolének and Weidermann [290] reported briefly on the ocular changes in a patient with macroglobulinemia and on two other patients with other kinds of paraproteinemia. Hanlon, Bayrd, and Kearns [291] commented on the severe engorgement found in the retinal vessels and the scattered exudates and the hemorrhagic zones seen in patients with macroglobulinemia. Ioli [292] reported a similar group of cases. Berneaud-Kötz and Nover [293] expressed the view that the changes in viscosity of the blood played an important role in the ocular changes. Donders, Imhof, and Baars [294] reported on a patient who had numerous small hemorrhages in the periphery of the retina associated with cryoglobulinemia.

Retinal Manifestations of Other Systemic Diseases

Snow [295] called attention to the clumping of the blood that occurs in the retinal veins if pressure is exerted on the globe with the thumb in the course of certain diseases and in pregnancy. Sometimes this phenomenon is associated with an increase of the erythrocytic sedimentation rate and of the serum globulins. Of 90 patients with this type of sludging in the retinal vessels, 79 had organic disease. These included 17 with active tuberculosis, 10 with carcinoma, 6 with sclerosis, 6 with bronchiectasis, and the remainder with such diseases as myelomatosis, fever of undertermined origin, pneumonia, rheumatoid arthritis, systemic lupus, reticulosis, leukemia, myocardial infarction, and ulcerative colitis. Amsler [296] showed a number of interesting serial photographs illustrating the chronologic development of various ocular lesions.

Oculocutaneous Syndromes.—Puscariu [297] discussed 16 cases, of which 10 were of the Harada syndrome, 4 of the Vogt-Koyanagi syndrome, and 2 of uveomeningitis. In all, the ocular manifestations appeared and developed during meningitis with hyperlymphocytosis, and there was bilateral uveitis. Of these patients, 12 had papilloretinal edema, 11 had neurodermatitis, 9 had dysacousia, 8 had retinal detachments, 4 had muscle palsies, and 6 had chorioretinitis. He believes that these diseases are caused by a neurotropic agent that affects the chromatophorotropic elements of the pituitary body and thus produces the depigmentation of the choroid, vitiligo, and poliosis. Tarab's [298] patient had an association of the Vogt-Koyanagi and the Klippel-Feil syndromes. Lieb and Guerry [299]

reported the occurrence of a severe exudative chorioretinitis in one eye of an infant who had incontinentia pigmenti (Bloch-Sulzberger syndrome) and noted that about 25% of the reported patients had ocular disturbances including strabismus, nystagmus, blue scleras, myopia, cataract, papillitis, retrolental fibroplasia, pseudoglioma, optic atrophy, and metastatic ophthalmitis. Gerth and Flegel [300] reported on a patient with hyalinosis cutis et mucosae who had multiple grayish patches in the retina. The photographs showed lesions that looked like ordinary hyaline bodies in the retina. Rosselet and Deller [301] reported on a patient who had a cutaneous nodule that proved to be angiosarcoma of Kaposi. It was their impression that the elevation in the retina that disappeared under x-ray treatment might have been a similar lesion. Hynie [302] reported a case of Grönblad-Strandberg syndrome in which the angioid streaks and the pseudoxanthoma elasticum of the skin showed no changes after 20 years of observation. Hermann [303] collected 225 cases of this syndrome and concluded that the inheritance of the disease was in the dominant mode. Larmande and Margaillan [304] reported on a patient who had angioid streaks, pseudoxanthoma elasticum, and Paget's disease.

Sarcoidosis.—Wegner and Wurm [305] wrote a monograph on Boeck's sarcoid and discussed 172 patients with ocular complications. Cremona and associates [306] reported on four patients with severe granulomatous uveitis.

Tuberculosis.—Konstas [307] examined 318 patients with pulmonary tuberculosis and found 43 who had pathologic changes in the fundus, most of them old. Amsler,[308] Witmer,[309] and Orozco Acuña and associates [310] discussed tuberculous lesions of the fundus. Dvorak-Theobald [311] reported on a patient who had fulminating tuberculous endophthalmitis, probably activated by desensitization therapy for hay fever. Kuo and Wu [312] discussed their treatment of macular tuberculosis and tuberculous scleritis and conjunctivitis. The lesions that had not responded to antibiotic or steroid therapy were successfully treated with x-ray irradiation.

Ocular Phakomatoses.—Iserle's [313] paper discussed the close relationship that exists between various of the ocular phakomatoses. Frequently, he stated, what appears to be a phakoma is in reality a vascular malformation genetically similar to von Hippel-Lindau disease. McIntosh Nicol [314] reported Lindau's disease in five generations: in the pedigree there were 4 cases of cerebellar cysts including 2 with proved hemangioblastoma, 11 of suspected intracranial tumor, and 3 of suspected pancreatic cyst. Golias-Makowska [315] reported three cases and Omulecka,[316] one case. Vail [317] reported on a case of angiomatosis retinae observed 11 years after successful diathermy and reviewed the literature, noting that similar therapy cured 70% of the cases reported. No new data appeared in the papers of Schwab,[318] Carenini,[319] and Nirankari and Maudgal.[320]

Other Neurologic Lesions.—An editorial [321] discussed the perivenous sheathing of the retinal veins first reported by Rucker in multiple sclerosis. Doden [322] found this type of sheathing in 30 of 130 patients with the disease. Cogan and associates [323] studied the eyes and optic nerves in two patients who died of metachromatic leukoencephalopathy. They found metachromatic substance in the cytoplasm of the larger retinal ganglion cells similar to the substance found in certain cells of the central nervous system. The optic nerves had clumping of what was interpreted as myelin. Raeder [324] and Hansen [325] reported bleeding into the retina after a subarachnoid hemorrhage. Stein and I [326] described the ocular findings in 47 cases of subdural hematoma, subdural hygroma, and subarachnoid hemorrhage among infants and young children. Sixty per cent of the patients had large retinal or subhyaloid hemorrhages or had extraocular muscle palsies or papilledema.

Miscellaneous.—Weve [327] described an interesting patient with chorioretinitis ra-

diata. Neubauer [328] and Veselý [329] discussed Jensen's juxtapapillary chorioretinitis. Musial [330] found that nitrogen mustard helped in the treatment of inflammatory diseases of the eye but was of questionable benefit in atrophy of the optic nerve and of no help in macular degeneration and retinitis pigmentosa. Féric-Seiwerth [331] treated 40 patients who had various fundus diseases, using 2% solution of isoniazid subconjunctivally. Twenty-three of these were cured, and seven remained unaffected. Cotta Dos Santos [332] treated his patients who had chorioretinitis and uveitis by doing a neurectomy of the carotid plexus, and this was successful in curing the disease in all 16 of them.

Noury, Oger, and Bouchel [333] reported on three patients with chorioretinitis, neurouveitis, and meningoencephalitis that proved to be of rickettsial origin. Successful treatment was given with Tifomycine in one case and Sanclomycine in another. Zimmerman and Johnson [334] demonstrated calcium oxalate crystals in the outer retinal layers of degenerated eyes and in cataractous lenses. These were best seen in sections with the use of polarized light and were identified histochemically. Pettinati [335] reviewed the inflammatory, neoplastic, and degenerative conditions that were accompanied by radiologic evidence of intrabulbar calcification. Wolter [336] reported the pathologic study of the retina in a case of secondary glaucoma and chronic uveitis.

Retinal Detachment

A very great number of articles have been written again during the past year on the subject of retinal detachment and its treatment. Nicholls and associates [337] participated in a symposium on this subject which cannot be well extracted. Lister [338] wrote a description of the entire field apparently for the benefit of the general practitioner.

Etiology.—Sánchez Bulnes [339] discussed the factors of race, age, sex, trauma, myopia, inflammatory lesions, vitreous changes, and aphakia. Vom Hofe [340] mentioned the influence of contusion of the globe. Schepens [341] described six types of retinal detachment caused by changes in the peripheral fundus: (1) classic dialysis in the young, (2) traumatic dialysis, (3) typical detachment observed after uncomplicated cataract extraction, (4) detachment after cataract extraction complicated by vitreous loss, (5) detachment after cyclodiathermy for glaucoma, and (6) subclinical detachment. Alfonso [342] expressed the view that there is a definite relationship between retinal detachment and arteriosclerosis. Osterczy [343] described retinoschisis in which the internal layer had a horseshoe tear and treatment was ineffective. Dufour and Bianchi [344] discussed retinal detachment in glaucomatous eyes. They observed that detachment only rarely occurs in an eye with high intraocular tension but more commonly when the tension has been reduced to low normal by medical treatment or operation. Bonavolontà [345] reported four detachments occurring in association with increased intraocular pressure and six in association with marked hypotony.

Methods of Examination.—Sutcliffe [346] directed attention to the value of projection perimetry in the detection of early retinal detachment. Ullerich and Krause [347] examined histologically an eye removed because of secondary glaucoma after occlusion of the central vein. There were marked retinovitreal adhesions to an area of destruction of the inner and middle retinal layers. Wolter and Jampel [348] reported histologic examination of an eye with retinal folds caused by an orbital sarcoma. Oksala and Lehtinen [349,350] described the use of ultrasonic energy in the diagnosis of retinal detachment.

Jacobson and associates [351] studied the electroretinogram among patients who had detached retinas and found that the amplitude of the b-wave was directly proportional to the excellence of the visual recovery. Asayama and associates [352] used a stroboscopic light to simplify the recording technique of the electroretinogram, and they showed that the a-potential as well as

the b-potential rose and fell parallel to the other clinical findings. They noted that the b-potential rarely recovered after reattachment. Rendahl [353] also discussed this subject. Schmöger [354] stated that a reduced electroretinogram in retinal detachment did not have prognostic value, and in all four of her patients the electroretinogram was reduced or negative and the results of surgical treatment were good or excellent.

Pathology.—Tamler [355,356] studied sections of eyes removed after detachment operations and described the healing of wounds, the reaction around the sutures, and the star folds in the retina. Hummelt [357] reported pathologic examination of two eyes enucleated two weeks and six weeks, respectively, after infolding of the sclera without excision. In both eyes the retina was firmly attached. Van Walbeek [358] reported a similar examination of eyes after operation. Cogan and associates [359] described the deposition of calcium oxalate and calcium phosphate crystals in the outermost portion of detached retinas. Alajmo [360,361] studied the viscosity of the subretinal fluid in 30 cases of idiopathic detachment and found no correlation between the degree of viscosity and the tendency to spontaneous reattachment or the success or failure of retinal detachment operations.

Surgical Techniques.—Landau [362] described the healing of a retinal detachment after retrobulbar injections of hyaluronidase. Tzanides and associates [363] reported on two patients who had spontaneous reattachment of the retina.

Picó [364] noted that, since 1950, there had been four major advances in the therapy of detached retina; these include (1) more accurate localization of tears, (2) binocular indirect ophthalmoscopy with scleral depression, (3) various forms of scleral resection or buckling, and (4) vitreous implants. There were a number of more or less general expositions of the subject.[365-368] Paufique [369] discussed the various aspects of and contraindications to surgical treatment. He mentioned the use of radiation to heal postoperative retinal exudates.

Paul and Fry [370] passed sutures through the sclera, choroid, and retina of the eyes of rabbits and later studied the histologic characteristics. They found that silk was well tolerated, chromic gut was not so well tolerated, and nylon caused a severe reaction. Arruga [371] described the Custodis and Schepens operations and then an operation in which he passed a nylon or Supramid suture through the sclera parallel to the equator. He tightened the suture after the subretinal fluid had been evacuated. Then he cauterized the tear by diathermy. Scleral resection was done if necessary, followed by injection of air into the vitreous if the globe remained soft. Sobhy [372] was able to visualize a retinal tear in a funnel-shaped retinal detachment by first aspirating the subretinal fluid and then injecting cerebrospinal fluid into the vitreous cavity until the eye resumed its normal shape. Five weeks later, scleral resection with diathermy was performed, leading to reattachment of the retina.

Meyer-Schwickerath [373] reported further on a total of 610 cases of all types, including cases of flat retinal detachment, in which treatment consisted of light coagulation. Ten Doesschate [374] discussed a similar technique. McDonald and Light,[375] and Guerry and associates [376] reported on their experience with photocoagulation of the retina. Strampelli [377] obtained five successes in eight cases of retinal detachment with macular involvement by giving ultraviolet treatment to the macula combined with injection of 18% solution of sodium chloride into Tenon's capsule, use of binocular bandages, and three to four days of rest in bed.

Henderson [378] and Clark [379] discussed the relative merits of scleral shortening procedures as contrasted to diathermy methods. Moreno Lupiañez and Casado Corzo [380] tested the effects of various intensities and durations of diathermy applications and came to the conclusion that there should be an area of lighter diathermy around an area of strong diathermy in detachment operations. Irvine and Knoll [381] studied the thermal effect of diathermy currents and, in an

excellent paper, discussed the various types of electric currents and their effects on the eye. Pritikin [382] advocated in some instances a multiple-type electrode. Madroszkiewicz [383] expressed the view that bipolar electrolysis is much superior to diathermy. Charamis [384] briefly discussed the incidence of retinal detachment after penetration of intraocular foreign bodies. He localized the tear in such cases, treated the area surrounding it with diathermy, and then incised the sclera in the center of the coagulation ring and extracted the foreign body through the tear in the retina.

Pischel and associates [385] participated in a symposium on scleral resection procedures. A number of other articles [386-389] discussed the use of sclerectomy. Dellaporta [390] discussed scleral buckling procedures. Schepens and associates [391,392] considered scleral buckling with an encircling polyethylene tube, with a partial polyethylene tube, without excision, or with a trap-door flap in the sclera. Hughes [393] produced a more permanent scleral fold by a single incision with dissection of the sclera and infolding of the inner scleral layer by means of an overlapping layer of the sclera. Shipman [394] described a method of enfolding the sclera. Black [395] has a similar modification.

Hitz [396] inserted polyethylene tubes and polyvinyl sponge in the subscleral space of dogs. Valcarce-Avello [397] described lamellar scleral resection with inclusion of the resected piece of sclera instead of a polyethylene tube. Lemoine and associates [398] and Grant [399] described imbrication of the sclera.

Shafer and Bussey,[400] Shapland,[401] and Moffatt [402] discussed the use of vitreous implants and called attention to their value in otherwise hopeless cases of retinal detachment. Oksala [403] injected air and saline solution into the vitreous of ox eyes. Because this sometimes destroyed the vitreous structure, it was suggested that, in operating for detached retina, air or fluids should not be injected into highly myopic or very old eyes, as the vitreous in such cases is most easily damaged.

In a very interesting and valuable paper, Schwartz [404] discussed postoperative ophthalmoscopic signs of success or failure. Jervey [405] favored early ambulation after retinal detachment operations, but some of his discussers disagreed with his views. Maione [406] discussed the causes of failure in detachment surgery. Colyear [407] urged that patients with retinal detachment be cured by diathermy alone if possible, as the visual end-results are better in patients of this group than in those treated by scleral resection. Basterra Ibarra [408] cured 9 of 15 patient who, he believed, would have represented failures without the scleral resections. Safar [409] successfully treated five of nine myopes who had a hole in the macula and retinal detachment by diathermy combined with retrobulbar implantation of human amnion. Šuster [410] used the same method.

Tumors of the Retina

Theobald and associates [411] reported on two eyes that had a proliferation of the retinal pigment epithelium and hyaline deposition causing diminished vision and subsequent enucleation because of suspected neoplastic changes. Fair [412] reported an ocular lesion described as a medulloepithelioma, said to have arisen from the pigment epithelium of the retina near the optic disc. Bierman [413] discussed two cases in which a tear was present in the retinal detachment overlying a malignant melanoma of the choroid. Blatt and associates [414] called attention to the remarkable resistance of the lens against the invasion of malignant tumors. Rosselet and Rosselet [415] discussed the excellent therapeutic results of radiation of intraocular metastatic malignant tumors. Kennedy and associates [416] described a metastatic carcinoma solely in the retina which had its origin in an adenocarcinoma of the rectosigmoid. Hotz [417] discussed hormone treatment of metastatic intraocular tumors with androgens, estrogens, cortisone, ovariectomy, adrenalectomy, and hypophysectomy. Hagedoorn and Salim [418] described disseminated deposits of pigment in other-

wise ophthalmoscopically normal areas of the retina as a manifestation of malignant melanoma, and Hagedoorn [419] demonstrated subretinal clusters of subnecrotic pigment epithelial cells ophthalmoscopically visible in a detachment secondary to malignant melanoma of the choroid.

Retinoblastoma.—A number of papers concerned the genetics of this disease. Böhringer [420] analyzed 100 cases, of which 95 were sporadic and 5 were in the second generation. He concluded that heredity is dominant with a penetrance of less than 50%. Therefore, heredity could play a role in the so-called sporadic cases. De Ocampo and associates [421] reported that the mortality rate is nearly 95% in the Philippines as opposed to less than 50% elsewhere. Twenty-three cases reported by Stevenson and Martin [422] from Northern Ireland were sporadic in each instance. Macklin [423] and Vogel [424] conducted similar studies. Moreno and associates [425] reported on 11 cases of retinoblastoma, in 2 of which the tumors were bilateral. Carbajal [426] reported 72 cases, of which 30% were bilateral. The mortality rate was 20% for those with unilateral disease and 52% for those with bilateral disease. The case fatality rate was considerably increased by delay in treatment. In bilateral disease, early enucleation of both eyes was safest, although enucleation of the first eye with early x-ray therapy of the other was successful in a few cases. When only enucleation of one eye was done in cases of bilateral disease, the mortality rate was 100%.

A patient reported by Küchle, Remky, and Sattler [427] had the clinical picture of hypopyon uveitis. There was a bullous detachment of the retina. The diagnosis of retinoblastoma was made by aspiration of the anterior chamber. Weizenblatt [428] described a boy of 8 years who presented the picture of severe uveitis and had a highly positive result with the dye test for toxoplasmosis, but who had a far-advanced retinoblastoma that caused the death of the child. Egleston and associates [429] reported the histopathologic examination of the eye and brain of a child who had retinoblastoma with extensive intracerebral extension, but whose presenting complaint had been that of trauma and intraocular hemorrhage. Ellison's [430] patient died of extensive metastasis to all parts of the body. The infant reported by Davis and Diamond [431] had calcified metastatic lesions of the skull and had a tumor but no calcification in the orbit.

Dunphy [432] reported eight cases of bilateral retinoblastoma in which the eye with more advanced disease was enucleated and the other eye, in which the lesions were small, was treated by diathermy to the tumor. This was effective in six of the eight patients. Meyer-Schwickerath and Helferich [433] treated 12 patients whose disease was bilateral by enucleating the first eye and using photocoagulation in the second eye. Of these, nine were cured, the tumor of one was histologically proved to be destroyed, and two patients did not respond because of an exudative retinal detachment. Joyce [434] reported on a 19-year-old youth whose left eye was removed at age 2 years because of retinoblastoma. The right eye became involved at age 19 and was treated and the disease cured by radon seeds.

Tamler, Winter, and Toch [435] had a patient with retinoblastoma that recurred in spite of treatment with x-rays, triethylene melamine, and locally applied radon seeds. Histologic examination showed that the sclera and optic nerve were radioresistant but that the ganglion cells and choroidal vessels were particularly radiosensitive. There were postirradiation changes also in the inner and outer nuclear layers of the retina, in the retinal vessels, and in the lens. Dias Alves [436] and Zoldan [437] emphasized the value of radioisotopes in therapy. El-Rifai [438] treated the second eye with nitrogen mustard and then by deep x-ray irradiation which eradicated the retinoblastoma.

Macular Lesions

Klien,[439] in an interesting paper, discussed the reaction of the retinal tissues, the pig-

ment epithelium, and the choroid to various affections and reviewed the differential diagnosis of lesions of inflammatory, degenerative, vascular, and neoplastic origin. Doggart,[440] in an excellent up-to-date review, classified the signs of macular disease as swelling, atrophy, vascular changes, newly formed connective tissue, crystalline deposits, alterations in the foveal reflex, and discoloration. The papers by Zachariah [441] and Law [442] were general reviews. Ehrich [443] stated that if the entoptic macular shagreen is absent, it indicates macular disease or amblyopia that cannot be improved. If the shagreen is merely abnormal, the macular disease or amblyopia is amenable to treatment. He said that the macular shagreen cannot be seen entoptically in massive vitreous hemorrhage, although the macula may be healthy. Goldmann [444] reported on two patients in whom the maculas appeared ophthalmoscopically to have simple edema, but biomicroscopically to have chorioretinitis. Honda [445] discussed the relationship between central serous retinopathy and Masuda's central retinitis. His arguments seem rather obscure.

Rados and Scholz [446] presented eight cases of heterotopia of the macula related to retinal lesions or folds, probably resulting from retrolental fibroplasia. Vizcarra [447] reported central serous retinopathy resulting from dental infection. Viefhues [448] described an 11-year-old boy whose twin was normal but who had unilateral aplasia of the macula, myopia, and myelinated nerve fibers in one eye. Carriker [449] reported disciform degeneration in a 22-year-old man. The patient of Gareis [450] had a cyst in the macula and a congenital crater of the optic disc, which seemed to be related. Van Bogaert [451] described a family tree of spastic heredoataxia with macular degeneration and with incontinentia pigmenti in some members of the family. Strobos and associates [452] reported on a family with cerebellar ataxia, dysarthria, and pigmentary degeneration, along with calcification of the basal ganglia as seen on x-ray examination.

Bialasiewicz [453] reported rapid improvement in the visual function of nine patients with central serous retinitis treated by retrobulbar injections of Priscoline. Csapody [454] cured three patients who had retinal detachment with macular hole by amnion implantation where diathermy coagulation had failed. Lipsius,[455] in discussing the treatment of senile macular degeneration, stated that the "patient should be given reassurance, and although treatment is empirical, a negative approach to therapy is unwise." Burnside [456] reported further on therapy of senile macular degeneration accomplished by suture of the inferior oblique muscle over the macula. All his 28 patients showed improvement, of marked degree in some. Stark [457] advocated the use of heparin as a treatment for atherosclerotic processes in the macula.

Degenerative Diseases of the Retina

The diversity of titles and subjects included in this section attests to the complexity of the processes that tend to be grouped under the general title of tapetoretinal degeneration. So far there is no satisfactory classification of these degenerations. Sorsby [458] spoke of abiotrophy as the primary difficulty in various of these degenerations. François and de Rouck [459] considered the differences in the electroretinographic patterns to be more significant in differentiating the types of tapetoretinal degeneration than are the visible changes in the fundi. François [460] discussed these differences in detail. François and de Rouck [461] reported that patients who have tapetoretinal degeneration, either peripheral or central, also have a bioelectric dysfunction of the retina and brain. The complete bioelectric syndrome is found in the peripheral degenerations: retinitis pigmentosa, retinitis punctata albescens, and choroideremia. Similar findings are present with central degeneration but are always less in amount. There are no such changes in senile macular degenerations. They stated that all of these degenerations have a common cerebroretinal feature, that is, a hereditary

abnormality in development of the prosencephalon.

Franceschetti and Dieterle [462] stressed the value of the electroretinogram. Ricci [463] claimed good results in 16% of cases, treating tapetoretinal degeneration with oxygen and vasodilators.

Retinitis Pigmentosa.—Kandori and Fujinaga [464] concluded that retinitis pigmentosa was caused by a primary disturbance of the endocrine glands, because in the serum of the majority of affected persons the values for glutathione, calcium, and cholesterol were lower than normal but rose after implantation of anterior pituitary lobe or thyroid tissue or both. Sakanouye [465] reported a low ratio of cholesterol to phosphate and a ratio of a-mucoprotein to b-mucoprotein that was similar to that present in arteriosclerosis. Goodman and Gunkel [466] found depressed scotopic electroretinograms in four children under 10 years of age who had no visible changes in the fundi but whose family had dominantly transmitted retinitis pigmentosa. Franceschetti and associates [467] described pigmentary degeneration of the retina associated with various viral diseases. Stucchi and Vollenweider [468] reported a case associated with Behçet's syndrome.

Donin and Crowley [469] reported on a patient with advanced retinitis pigmentosa in whom choked discs developed because of intracranial metastatic carcinoma. The center of each disc was elevated, but the margins of the disc were flat and had a rosette of hemorrhages. Vrabec [470] reported a case of unilateral pigmentary degeneration of the retina. Alberth and associates [471] studied the hearing of 17 patients and found a nerve-deafness type of hearing loss in all. It was proportionate to the loss of visual field. They thought the relationship might be due to involvement of the diencephalon.

The association of primary pigmentary degeneration of the retina with various neurologic states is illustrated by the case reports of the following diseases: Refsum's syndrome of heredopathia atactica polyneuritiformis [472]; acanthrocytosis and heredodegenerative neuromuscular disease [473]; external ophthalmoplegia and complete heart block, by Kearns and Sayre,[474] and the Laurence-Moon-Biedl syndrome, by Ross and associates [475] and Barut and associates.[476]

The search for treatment continues. Alberth [477] discussed a number of different methods. Papst and Heck [478] found an increase in the b-wave in the electroretinogram when nitroglycerin, Nepresol, or dextrose was given but not when oxygen was administered. Gordon and Burke [479] examined several patients whose condition was said to have improved under treatment by others with Dicumarol; they could not confirm the claims about this treatment nor did any of their own patients manifest improvement with anticoagulant therapy. Miron and associates [480] reported improvement after pilocarpine instillations and orally administered nicotinic acid. Guist [481] reported improvement following extirpation of the stellate ganglion and injections of retinal extract (cellulin retinale) in six cases. Sakanoue [482] reported improvement after removal of the coccygeal body which was said to cause a decrease in the cholinesterase activity in the blood and spinal fluid. Campos [483] introduced a strip of muscular tissue from the medial or lateral rectus into the suprachoroidal space of eight patients with retinitis pigmentosa and claimed there was improvement. Alberth [484] discussed the extraction of cataract in patients whose vision is reduced.

Miscellaneous Degenerations.—Reese and Straatsma [485] reported 17 cases of retinal dysplasia, a diffuse developmental aberration affecting both eyes and associated with anomalies of the central nervous system and of other systems of the body. The ocular malformations consist of microphthalmos, shallow anterior chamber, remnants of pupillary membranes, and synechias. There are mild cataracts, but the prime feature is a white retrolental mass formed of dysplasic retina associated with irregular rosettes, retinal detachment, and persistent primary vitreous. The filtration angle is

of fetal type, and these eyes are subject to glaucoma and intraocular hemorrhage. Appelmans and Michiels [486] reported on four patients of apparently the same type. Alström and Olson [487] published a very interesting study of 105 families in which there were children with congenital blindness. There were few objective signs in early life, although later there were pigmentary degeneration of the retina, cataracts, optic atrophy, and keratoconus. The cases reported by Waardenburg [488] are apparently similar to those described by Alström and Olson.

Franceschetti and Forni [489] reported on three patients in one family with tapetoretinal degeneration and marbling of the peripheries of the retina. Jöhr [490] described a family in which four of nine children were blind. There were waxy pallor of the optic disc and peripheral pigmentation of the retina. Feigenbaum [491] reported on two patients with Oguchi's disease who had the typical grayish discoloration of the retina after exposure to light and a normal fundus after several hours in the dark.

Chams and Sadoughi [492] described two cases of gyrate atrophy. Pajtáš [493] reported on a family with three members who had honeycomb degeneration of the retina. Karpe and Zetterström [494] reported four cases of a previously undescribed eye disease demonstrated by electroretinography and called "congenital retinal dysfunction." There was severe reduction of visual acuity, but the fundi were said to be within normal limits and the optic discs of good color. However, there was some deficiency of pigmentation of the retina which had a granular yellowish appearance and poorly defined macula.

Hervouet [495] wrote a paper illustrating the degenerative lesions of Bruch's membrane and of the pigmented cells of the retina. Forni [496] presented a new genealogic tree of central tapetoretinal degeneration (Leventine disease). Lisch [497] reported on two families containing three members, each affected with tapetoretinal degeneration in the lower half of the fundus. Bégaux and Decock [498] described a new pedigree of Steinert's myotonic dystrophy in which several members had degenerative retinal foci consisting of a brick-red fovea surrounded by a zone of increased light reflexes. Favre [499] described a brother and sister who had degeneration of the hyaloid and retina.

Toxic and Other Injuries to the Retina

There are three reports on the toxic effects of N. P. 207 (3-chloro-10-[2-N-(methylpiperidyl) ethyl] phenothiazine). Wright [500] discovered that toxic retinopathy developed in 28 of 32 psychiatric patients to whom this drug was administered for four to five weeks in an average daily dose of 400 mg. Six of these patients became practically blind. The retinal changes consisted of deposits of brownish-black pigment. Rintelen, Hotz, and Wagner [501] found similar changes in their patients but could not reproduce them in animals. Burian and Fletcher [502] studied two patients who sustained pigmentary retinal degeneration after the administration of N. P. 207 and found severe toxic damage to both rods and cones, with extremely delayed dark adaptation.

Sorsby and Nakajima [503] tested a number of diaminodiphenoxyalkanes, agents being tested for the treatment of schistosomiasis, and found that intravenous administration of very small single doses to rabbits produced a marked degeneration of the visual cells and pigment epithelium of the retina. Ashton [504] tested a substance of this group known as M & B 968A (1:5-di [p-aminophenoxy] pentane dihydrochloride) on monkeys and cats, finding focal swelling of the pigment epithelium and degeneration of the retina. These changes resembled the toxic retinopathy caused by iodates. Sorsby and Nakajima [505] found that sodium cyanide and sodium fluoride given intravenously to rabbits produced marked retinal degeneration in about one-fifth of these animals. Óta [506] demonstrated degeneration

of the retina due to potassium and sodium iodate.

Mosquera and Accame [507] reported on two patients with myeloid leukemia in whom 6-mercaptopurine therapy caused toxic amblyopia. The vision recovered when treatment with the drug was stopped. Matsumoto [508] produced degeneration of the retina and optic nerve with aspidium extract in mice. This degeneration was much more severe in animals deficient in thiamine. Oliver and Havener [509] described a very interesting patient, aged 14, in whom chronic vitamin A intoxication developed after 10 months' therapy of acne vulgaris with 200,000 units daily. There were increased intracranial pressure, with choked discs and retinal hemorrhage, loss of hair, cutaneous eruptions and pigmentation, pain in the bones, generalized malaise, and hypomenorrhea. They presented data on 36 other patients who had some or all of these signs; some of them had enlarged liver and spleen, and some had exophthalmos.

Gerber [510] reported on two patients with toxic visual signs caused by digitalis overdosage. She reviewed the symptoms of digitalis intoxication, which include yellow, green, blue, and red chromatopsia as well as flickering, dimness of vision, scotomas, visual hallucinations, conjunctivitis, nystagmus, mydriasis, and exophthalmos. Reiter [511] described the entoptic phenomenon of blue spots, which he called "cornflower phenomenon," caused by digitalis. Bialasiewicz [512] saw six patients who became partially or totally blind after the drinking of an unknown solution prepared by a local medicine man in Indonesia. Priscoline given into the retrobulbar region was effective in the early stages but not in the late. Stanković and Kecmanović [513] and Slem and Bastüzel [514] described patients with visual loss due to sensitivity to quinine.

Klenová and Fantiš [515] investigated the treatment of methyl alcohol poisoning with ethyl alcohol, as recommended by Roe, and concluded that this treatment was too dangerous for practical use. BAL (dimercaprol) did not prevent destructive changes in the optic nerve. Cysteine helped only partially. High doses of ascorbic acid completely prevented the deleterious effects of alcohol, and the authors recommended that it be used in clinical practice. Lasco [516] reported two cases of optic atrophy following ingestion of methyl alcohol. Sédan [517] observed very rigid vascular trunks near the optic disc as the initial sign of poisoning by ethyl alcohol.

Ambrosio, Marsico, and Piccoli [518] reported on 23 patients with vascular disease caused by exposure to carbon disulfide. These were all workers in the rayon industry, and symptoms consisted of headaches, vertigo, and asthenia. The retinal arterioles became tortuous and thickened, and there were cotton-wool patches. Electroencephalograms showed a diffuse abnormality in the subcortical structures. Ide [519] produced degenerative changes in the ganglion cells and the optic nerve in mice with carbon disulfide.

Funder [520] described a case of siderosis of the eye. Karpe [521] recorded electroretinograms in 43 eyes with intraocular foreign bodies and expressed the opinion that the electroretinogram is useful in the diagnosis of incipient retinal siderosis and can aid in the surgical decision. Appelmans and associates [522] stated that copper, no matter how small the piece, should always be removed from the eye. In addition to deposition of copper salts in Descemet's zone and to sunflower cataracts, they described destruction and granular deposits in the vitreous and glittering, sharply outlined retinal lesions. Kajikawa [523] produced toxic amblyopia with lead in mice and found that animals deficient in thiamine have more severe changes in the optic nerve than those with normal thiamine levels. Montero Marchena [524] reported on a patient with toxic amblyopia from lead; treatment with cocarbyl and nicotinic acid led to total recovery.

Jayle and associates [525] and Bengisu and Basar [526] reported cases of tobacco-alcohol amblyopia. Cartasegna [527] treated 22 pa-

tients who had tobacco-alcohol amblyopia with intravenous Periston "N" and obtained excellent results in younger patients but not in the older ones.

Svoboda[528] described the fundi of a family of five who were exposed to the effects of gas for a month. Each had striking tortuosity of the retinal vessels, and one child had edema, peripapillary exudate, and hemorrhage, while two children had atrophic and degenerative retinal changes. Cruickshank[529] reported on 100 patients with a syndrome consisting of upper-motor-neuron lesions, damage to the first sensory neuron in the peripheral nerves or posterior columns or both, retrobulbar neuritis, and eighth-nerve deafness with a gradual onset. It was ascribed to dietary deficiency. Krikler and Schrire[530] reported on a patient in whom severe malnutrition developed, with reddening of the hair and retrobulbar neuritis, after a surgically constructed blind loop in the ileum.

Neubauer[531] analyzed the mechanical factors involved in injury to the posterior part of the globe by indirect contusion: (1) the action of contusion on the retina (contrecoup); (2) the disfigurement of the eyeball which causes rupture of the choroid, whose site is presumably near the entrance of the posterior ciliary vessels, and (3) the sudden shift of the eyeball. Dollfus and Michaux[532] reported the case of a woman who tried to enucleate both eyes with her fingers, but the pain was so great that she fainted and became blind through bilateral and total retinal detachment with vitreous hemorrhage. Bonnet[533] reported on a patient with extensive hematoma of the orbit, causing obliteration of the central retinal artery and retinal hemorrhage.

Preobrasensky[534] reviewed the international literature on chorioretinal injuries from atom bombs. A similar article was written by Brown.[535] Winter and associates[536] reported the effect of various amounts of high-intensity γ-radiation in the cat. This very interesting article should be read in the original.

Optic Nerve

There is a very large literature on the various affections of the optic nerve. Some of these have been covered in the annual review of neuro-ophthalmology. Two general articles are of interest: that of Carroll[537] and that of Mooney.[538] Neither can be well abstracted, and they should be read in their entirety.

Anatomy.—Rucker[539] discussed in an interesting paper the historical development of the concept of semidecussation of the optic nerves. Wiegand[540] demonstrated by casts of both optic canals the three-dimensional anatomy of this structure and showed methods of visualizing the canal radiographically. Blatt and Athanasiu[541] studied the radiologically demonstrable relationship between the optic canals and the sphenoid sinuses. Watson[542] discussed radiographic examination of the optic canals. Slade and Weekley[543] reported a case in which the right optic nerve was divided in two by an abnormal branch of the right internal carotid artery. Brégeat[544] discussed fractionated air encephalography to visualize the anatomy and changes about the optic nerve. Hughes[545] correlated anatomic information of the blood supply of the optic nerve and chiasm with the clinical findings in several interesting cases.

Traumatic Lesions.—Pasino[546] and Kleinert[547] each reported a case of traumatic avulsion of the eye and optic nerve with visual defects in the uninjured eye due to chiasmal damage. Colombo Bolla[548] reported on a patient who, after optic nerve injury, recovered good vision but did not recover a direct pupillary light reflex. The consensual reflex was preserved. Dejean and associates[549] discussed seven cases of optic atrophy after orbital injury. Montauffier and Camo[550] reported eight such cases, in almost all of which the loss of vision was immediate. Treatment was with retrobulbar vasodilators, and the vision returned with only mild permanent loss. They stated that surgical treatment should be reserved for patients with chiasmal lesions. They expressed the view that these lesions

of the optic nerve are vascular in origin. Babel [551] presented a case in which electroretinographic studies were made, and he agreed that the abnormalities are vascular ones.

Inflammatory Diseases.—A very comprehensive review of the subjects of retrobulbar and optic neuritis is presented in the symposium by Lazorthes and associates.[552] The determination of the etiology of the disease is a difficult problem, as few of these cases are proved and the matter of etiology is largely a matter of association and conjecture. Also the method of treatment is difficult to assess in view of the tendency toward recovery of vision without treatment in most cases of inflammatory disease of the optic nerve. Sasso [553] reported a case of optic neuritis that accompanied varicella and was cured by treatment with vitamin B_1, Priscoline, cortisone, and chloramphenicol. Turnbull [554] reported a case following about 10 days after an episode of thoracic pain and high fever said to be Bornholm disease, a viral disease of the Coxsackie-B type. He claimed dramatic improvement from steroid therapy, and yet the course of recovery was about the average for that of untreated optic neuritis.

Deller and Streiff [555] described a case of unilateral atrophy of the optic disc following an acute retrobulbar neuritis in the course of Q fever. De Vincentiis [556] could not demonstrate viral agents with laboratory tests in any of 11 cases of retrobulbar neuritis, clinically considered to be of viral origin. Frugh and Rabiner [557] described papilledema with normal vision as one of the manifestations of polyneuritis of the Guillain-Barré type. The total proteins in the spinal fluid measured 210 mg. per 100 cc. Mollica [558] recommended drainage of the ethmoidal and sphenoidal sinuses in certain cases of retrobulbar neuritis, and Vaighel [559] reported a cure obtained by removal of infected tonsils. The patient of Pannarale [560] had an acute bilateral retrobulbar neuritis with paralysis of the medial rectus and superior oblique muscles of the right eye along with herpes zoster of the fourth cervical nerve. Oral therapy of diabetes in the patient reported by Purtscher [561] caused toxic-allergic complications including headache, paresthesias, rhinitis, and bilateral papillitis, leading to secondary optic atrophy of the left eye. Cessation of treatment was followed by quick recovery.

Lorentzen [562] reported on a patient with pernicious anemia who had bilateral retrobulbar neuritis. Imachi and associates [563] produced optic atrophy by either vitamin A or vitamin B_1 deficiency in mice. A deficiency of these substances apparently seriously aggravates the damage caused by toxic substances such as acetic lead and aspidium taken by mouth. These authors stated that as multiple sclerosis is a rare disease in Japan, probably few cases of retrobulbar neuritis there are on that basis. Peters [564] discussed nine patients with systemic atherosclerosis who sustained optic neuritis on an arteriosclerotic basis.

Săbădeanu and associates [565] reported bilateral optic neuritis during the course of lactation. Kepes and Remenár [566] reported a similar case but decided it was due to multiple sclerosis. Misar,[567] Hugonnier and Paufique,[568] and Noto [569] reported cases of retrobulbar neuritis in which the etiology was not determined. Twenty-three of Noto's twenty-six patients had complete visual recovery after spinal puncture, cerebrospinal pumping, and injection of calcium compound into the carotid artery.

Welch and Cooper [570] reported on 21 patients among whom were found various complications of cataract extraction including macular edema, papilledema, and optic atrophy. They postulated that macular edema and papilledema resulted from a change in the vitreous, from hypotony, or from both, while optic atrophy could result from a vascular insufficiency at the disc. Reese and Carroll [571] had 17 patients in whom optic neuritis appeared from the 6th to the 12th week after an uncomplicated intracapsular operation for cataract. Only six of these had a good return of vision. Presumably these were cases of ischemic optic neuritis, but in only three was the

diagnosis of temporal arteritis excluded by biopsy.

Henderson [572] presented 6 of his own cases and 10 from the literature in which he proposed the term "optic neuropathy of Graves' disease" to describe the visual disorder which was manifested by either central scotoma or defects of the nerve-fiber bundle. The majority of patients recovered useful vision no matter what treatment was used.

Taylor [573] discussed the differential diagnosis of papilledema and optic neuritis, and their clinical symptoms and etiology. Kurz [574] reviewed the ophthalmologic signs of intracranial lesions. He emphasized that a central scotoma occurring in the visual field should not be considered a certain sign of multiple sclerosis. It could very well be the first manifestation of an intracranial tumor.

Saldún De Rodriguez and associates [575] surveyed 75 cases of tuberculous meningitis. They found changes in the optic disc in 46 of these, including 32 with papilledema and 21 with pallor. There were 5 patients who had choroidal tubercles and 31 who had disturbances of ocular motility, including pupillary abnormalities. Of 42 patients checked for visual disturbances, 17 had amaurosis, diminution of visual acuity, and either hemianopia or concentric contraction of the fields.

Van Zeben and Verbiest [576] stated that blindness as a complication of tuberculous meningitis still exists in spite of modern therapeutic agents and that surgical therapy is indicated in some cases. Blagojević and Arambasić [577] studied 250 cases, of which 40 were seen at necropsy, finding interstitial perineuritis, hydrocephalus, and cerebral edema as factors in the visual symptoms. Papilledema was present in 23% of their cases and optic atrophy in 2.8%. Tokareva [578] treated 20 children who had optic atrophy from tuberculous meningitis with atropine, retrobulbar injection of strychnine, stimulants, aloes, preserved blood, and placental tissue, together with streptomycin and para-aminosalicylic acid (PAS) by iontophoresis along with parenterally administered streptomycin and PAS.

Klíma and associates [579] and Lascu and associates [580] discussed the relationship of tuberculosis with opticochiasmal arachnoiditis. Bećirić and Stanković [581] found among their 49 patients with opticochiasmal arachnoiditis that 23 had retrobulbar neuritis, 13 had optic atrophy, 7 had papilledema, and 6 had normal optic nerves. Of the 49 patients, only 11 had a diagnosis as to etiology: 4 had paranasal sinusitis, 3 had experienced trauma, and 4 had tuberculosis or syphilis. Neurosurgical treatment improved the visual acuity. Imachi [582] expressed the view that opticochiasmic arachnoiditis causes secondary optic neuritis by disturbing the circulation of the spinal fluid. Porrúa López and Carrión [583] reported 15 cases of opticochiasmic arachnoiditis.

Some methods of treatment are described for inflammatory lesions of the optic nerve. Ardouin and associates [584] discovered by neurosurgical means that a case of visual loss was caused by acute edema of the optic nerve. No meningoencephalitis or arachnoiditis was found, and the optic nerve was very thick. Two years later, the other optic nerve presented the same type of acute edema. Similar surgical treatment restored good sight on both sides. Rehák and associates [585] reported good improvement in cases of optic neuritis when vitamin B_{12} was administered. Bayet, Brihaye, and Van Geertruyden [586] injected hydrocortisone into the retrobulbar tissues of four patients. Improvement was immediate, and recovery occurred in 7 to 14 days. Riser and associates [587] treated 10 patients who had optic neuritis by sympathectomy; 4 whose neuritis was of alcoholic origin were greatly improved, while 1 whose neuritis was of unknown origin and 1 whose neuritis was of syphilitic origin had stabilization, but in the 4 remaining patients treatment failed. In the last-mentioned patients the optic neuritis was caused by syphilis, arsenic, and Biermer's disease.

Optic Atrophy.—Imachi and associates [588] found not only chiasmal but widely spread

arachnoiditis in 32 patients who had Leber's disease and were subjected to craniotomy. Kwittken and Barest [589] reported histologic study of a patient who had had Leber's disease and died. There were marked atrophy of the ganglion-cell layer and some atrophy of the inner nuclear layer. The optic nerve was very atrophic but without inflammatory infiltration. The optic nerves, tract, and chiasm showed a severe degree of symmetric destruction of the myelin sheaths and axis cylinders. Both geniculate bodies had marked cellular atrophy but the calcarine cortex and pituitary glands were normal. Iverson [590] reported on a family that included five patients with hereditary optic atrophy in four generations, with a dominant mode of transmission. Manchester and Calhoun [591] described an interesting family afflicted with dominant hereditary optic atrophy in which several of the afflicted members had bitemporal hemianopic defects. Junceda Avello [592] expressed the view that infection is a factor in Leber's disease and that cases of chiasmal arachnoiditis may be secondary to the optic atrophy.

The reports of Farnarier, Arnoux, and Gérin,[593] of Horstmann,[594] and of Hahn [595] pertain to syphilitic optic atrophy. Gregersen [596] reported optic atrophy in a 3-month-old, otherwise healthy, breast-fed child. When this child was 2 months of age, the mother was treated for tapeworm with aspidium. The author suggested that this caused the optic atrophy. Breast-feeding had been interrupted for only 36 hours. Bell [597] discussed the question of diabetic optic neuropathy. Shaw and Duncan [598] reported on a family in which two members had diabetes, nerve deafness, and optic atrophy, while a third had diabetes, nerve deafness, and normal vision.

The papers of Espildora-Luque,[599] Georgiades and Anastassiades,[600] and Piper and Unger [601] discuss the loss of vision that follows repeated distant hemorrhage.

Newell and Beaman [602] reviewed the ocular manifestations among 143 patients who had intracranial meningiomas. This article should be read in its entirety. Meadows [603] described 15 cases of meningioma and 7 of aneurysm among others in which unilateral compression of the optic nerve was found. Petit-Dutaillis and associates [604] and White and Foltz [605] reported on optic atrophy caused by intracranial aneurysms. Vanni [606] described multiple bony chondromatosis followed by optic atrophy due to bilateral chondromas of the sphenoid sinus. Lyle [607] discussed the effect of injury to the optic nerve and suggested some avenues of research directed toward recovery of function of the nerves. Daxnerová [608] and Kearns and Rucker [609] described patients with chromophobe adenoma of the pituitary gland. The former author's patient had both a chromophobe adenoma and a meningioma of the sella compressing the left optic nerve. The patient of Kearns and Rucker had arcuate scotomas in the visual field rather than the classic bitemporal field defect.

Pietruschka [610] described five cases in which there was a combination of optic atrophy, exotropia, exophthalmos, and marble-bone disease. Viallefont and associates [611] reported 90 cases of leukemia, in 29 of which there was either papilledema or optic atrophy. Lyle [612] discussed the visual loss arising from arteriosclerotic changes in the vessel to the chiasmal and prechiasmal pathways, and Bynke [613] found the syndrome of Foster Kennedy in 16 of 1,600 patients with cerebral disease. He emphasized the restricted diagnostic value of this syndrome. Lasco and Nicolesco [614] discussed the syndrome of excavation of the lamina cribrosa (so-called pseudoglaucoma) and found a variable etiology including methyl alcohol toxicity, sclerosis of the internal carotid artery, temporal arteritis, sclerosis and hypertension or hypotension of the general arterial pressure, and intracranial or orbital tumors.

Redslob [615] expressed the view that in chronic primary glaucoma the optic atrophy begins first in the intracranial portion of the optic nerve and then progresses from the chiasm to the globe. Petersen [616] re-

ported on 30 patients who had colloid bodies in the optic nerve, 7 of whom had progressive increase in the number of these bodies. Wolter [617] found degenerated nerve fibers showing pearl-like thickening of their myelin sheaths and axons in an atrophic optic nerve.

Papilledema.—Fronimopoulos and associates [618] discussed the problem of pseudopapilledema. Huber and Cagianut [619] distinguished choked disc from the papilledema of malignant hypertension. Dubois-Poulsen and Magis [620] reported on 13 patients whose blind spots were enlarged but who had no ophthalmoscopic changes to account for them. Two had had intracranial trauma, two had aneurysms, four had pituitary adenomas, one had noncystic craniopharyngioma, one had a cystic tumor of the third ventricle, two had enlarged ventricular systems, and one had an expanding lesion of the left temporo-occipital region. El-Araby and Hosni [621] pointed out that early papilledema may start as a retinal hemorrhage before the papilledema appears. Esteban [622] discussed the significance of the disappearance of the venous pulse in increased intracranial pressure. Salgado Gómez [623] stated that the electroretinogram was of value in differentiating optic atrophy of the descending type from that of the ascending form. They found the electroretinogram almost invariably normal in papilledema. Paraicz and Bauer [624] reported on 467 patients with cerebral tumor, among whom 70% had choked discs. The degree and frequency of papilledema were less for frontal and parietal tumors than for temporal and occipital ones. In pontocerebellar tumors the amount of papilledema was greater on the side of the tumor.

Roper-Hall [625] described five patients in whom papilledema was present even though the intracranial pressure was normal. He ascribed the papilledema to a gradual decrease in nutrition and oxygen supply. Among 16 patients with choked discs examined by Dreyer,[626] 5 were followed for a long time, and the decision was reached that these represented physiologic variants. In two patients arachnoiditis was verified by exploration, and in five it was diagnosed clinically. In three patients the choked discs were the result of aseptic sinus thrombosis, and in one the diagnosis was obscure. In these 11 patients the papilledema diminished without decompression and without visual impairment. Appaix and associates [627] reported on a child 6 years old in whom choked discs developed in the course of bilateral otitis media. Recovery followed bilateral mastoidectomy. Novotný and Dostál [628] reported on nine patients with nontumoral intracranial hypertension. Mérei and Donáth [629] reported on patients with thrombosis of the intracranial sinuses. Of 24 such patients, 3 had choked discs, 1 had venous hyperemia, and 1 had retrobulbar neuritis. Tosello [630] reported on a patient with bilateral papilledema which was interpreted as resulting from thrombosis of the superior sagittal sinus caused by maxillary sinusitis.

Levatin [631] described a patient who had markedly elevated intracranial pressure and bilateral optic atrophy but no papilledema. The cause was a glioma arising in the chiasmal region and compressing the optic nerves, presumably blocking the optic foramina. Starr, Stroebel, and Kearns [632] reported that of 106 patients with infratentorial vascular tumors, 38 (36%) had hemoglobin values of more than 15 gm. per 100 ml. of blood and 11 had values of more than 18 gm.; 10 of the 11 had papilledema. Therefore, they concluded that polycythemia with papilledema should suggest a vascular tumor of the posterior fossa. Leggat [633] reported papilledema as an accompaniment of gross pulmonary emphysema. Gass [634] and Ladwig and associates [635] reported papilledema as a complication of poliomyelitis.

Glioma and Other Tumors.—Of 46 patients described by Dodge and associates,[636] 12 had gliomas of the optic nerve and 34 had diffuse or chiasmal gliomas. In the former group, proptosis was the commonest finding; in the latter, bilateral loss of vision. Most were low-grade astrocytomas with a

few oligodendrogliomas and ganglioneuromas. All tended to spread toward the optic chiasm. Surgical removal of the optic-nerve gliomas with preservation of the globe, if not involved, was the treatment of choice. Nover and Zielinski [637] studied 30 orbital and 25 optic-nerve tumors with essentially similar findings. They pointed out that tumors of the nerve almost always enlarge the optic foramen, while orbital tumors rarely do.

Fowler and Matson [638] reported on four patients with intraorbital and nine with intracranial gliomas. All nine presented x-ray evidence of an abnormality of the skull. Boles and associates,[639] Hager,[640] Dybicka and associates,[641] Jain,[642] Jaensch,[643] Oribe and Zimman,[644] Labib,[645] Paiva,[646] and Haberland [647] all reported on gliomas of the optic nerve. Böck and Kraus [648] recommended a large orbitotomy incision with resection of the retrobulbar part of the optic nerve as an initial step. Then after histologic confirmation of the tumor, resection of the intracranial part of the nerve follows. This procedure avoids intracranial operations in nonneoplastic disease, and the eyeball is not removed. Liss and Wolter [649] described the pathology of a glioma of the optic nerve, which proved to be an oligodendroglioma.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Harold G. Scheie, M.D., Chairman
William E. Krewson III, M.D., Clerk

Oct. 23, 1958

Functional Results with Contact Lens in Unilateral Congenital Cataracts with High Myopia. Dr. Philip G. Spaeth (by invitation).

The paper deals with the optical, physiological, and some of the routine problems otherwise associated with the above heading. The importance of early treatment because of associated amblyopia is stressed. Contact lenses are used in these patients to minimize the aniseikonia which is necessarily present. The functional results of the patients, i. e., percentage of patients with first- , second- , and third-degree fusion near and far is the main essence of the paper. Seventy-four per cent of those patients satisfactory for contact lenses obtain third-degree fusion.

Retained Glass Foreign Bodies in the Anterior Chamber. Dr. P. Robb McDonald and Dr. Mila J. Ashodian (by invitation).

Four cases of particles of glass in the anterior chamber are presented. Three of them were unrecognized at the time of the accident, one for 9 years and one for 13 years. They all had a history of injury in which glass was involved, and all demonstrated photophobia, blurred vision, and corneal edema. One case also had a persistent mild iridocyclitis. Gonioscopy proved the only satisfactory method to identify these foreign bodies.

Operative removal of the foreign body resulted in remission of symptoms and clearing of the corneal edema but, as to be expected, persistence of the corneal scarring. At operation, a large 150 degree and 180 degree corneal section must be made and the cornea may have to be folded on itself, so that the surgeon can see the angle. A loupe or operating microscope may be necessary to visualize the foreign body, once the angle is exposed.

It is important to gonioscope all patients who give a history of ocular injury involving glass. Failure to detect glass after such an injury may result in loss of compensation benefits to the patient, and other legal entanglements.

Retinal Folds in Orbital Expanding Lesions. Dr. Thomas R. Hedges Jr. and Dr. I. H. Leopold.

This paper describes two patients with orbital expanding lesions who showed typical parallel retinal folds or corrugations of the posterior pole. The orbital pathology was due to fibrous dysplasia in one and metastatic hypernephroma with metastasis to the orbit in the other. The characteristics of this type of direct impression of the globe from an intraorbital lesion are described in detail, and the literature is reviewed. It is emphasized that these folds probably occur much more frequently than they are described and occur in a multitude of conditions, including non-neoplastic forms, such as exophthalmos associated with thyroid disease.

Cataract Extraction by the Modified Smith Technique. Dr. Richard A. Ellis.

This report described the method of intracapsular cataract extraction developed and performed by Sir Henry Holland in India and Pakistan.

The methods of intracapsular cataract extraction developed by Colonel Henry Smith were reviewed and three illustrative diagrams shown. Then the method developed by Sir Henry Holland was demonstrated with diagrams and photographs taken during cataract surgery. In essence, the modified Smith technique developed by Sir Henry Holland is one which delivers the cataract intracapsularly by means of external manipulation. However, the following limitations and contraindications are considered most essential:

1. This procedure should not be attempted in a plethoric, short-necked, corpulent, tense person.

2. It should not be attempted in so-called dangerous eyes ("ox-eye"), such eyes in which the upper lid cannot be lifted easily from the globe, as in high myopia or exophthalmos.

3. It should not be performed in cataracts of young adults under 45 to 50 years.

4. It should not be performed in cataracts associated with glaucoma.

5. It should not be performed if there is any evidence of positive pressure after the anterior chamber is entered.

6. If legitimate pressure does not succeed in dislocating the lens, this method should not be further pursued.

7. It should not be used in congenital, traumatic, and complicated cataracts.

Adhering to the above limitations, Sir Henry Holland and his son, Ronnie Holland, have obtained excellent results in cataract surgery. They believe that vitreous loss is not over 2% and that fewer lens capsules are broken. Another advantage of this procedure is that no instrument is put into the anterior chamber of the eye. This is especially important in cases of endothelial dystrophy, since no instrument touches the posterior corneal surface. It may also decrease the possibility of postoperative infection.

Correspondence

SUPERFICIAL KERATITIS DUE TO PLASTIC FOREIGN BODIES

To the Editor:—I refer to the article by Dr. Duane, "Superficial Keratitis Due to Plastic Foreign Bodies" (A. M. A. ARCH. OPHTH. 61:141 [Jan.] 1959).

Such particles, sometimes whole clusters of them, are seen very often in the Eye Clinics of the Garment Workers Union here in New York. I have nothing to add to the fine description in the article. The treatment recommended there is removal with metal spud or needle, as "they will not dislodge with cotton swab."

I would like to note that they are dislodged easily by wiping with a fine blunt-pointed wet cotton-on-wood applicator, if wiping is done with slight pressure. There was not one particle to resist dislodgement in this way. There are never abrasions or scratches. The cornea shows after removal of the foreign body only a faint outline of the place where the particle has been.

JULIUS KESSLER, M.D.
229 E. 79th St.
New York 21.

News and Comment

SOCIETY NEWS

International Society for Clinical Electroretinography Formed.—During the International Congress of Ophthalmology held in Brussels in September, 1958, an International Society for Clinical Electroretinography (ISCERG) was organized. The objective of the Society is to promote the work in clinical electroretinography by preparing and conducting meetings and symposia, by establishing a central bibliography distributed regularly to the members, and by suggesting a standardization of the instrumentation and procedure in clinical electroretinography and of the recording and measurement of clinical electroretinograms.

The work of the Society will be carried out by a Central Board of Officers, a General Committee, and an Advisory Board.

The officers of the Society are as follows: President: G. Karpe (Stockholm); Vice-Presidents: A. Franceschetti (Geneva) and J. François (Ghent); Secretary-General: H. E. Henkes (180 Schiedamsevest, Rotterdam, Netherlands); Secretary for the Western Hemisphere: H. M. Burian (Department of Ophthalmology, University Hospitals, Iowa City); Treasurer: W. Straub (Universitäts-Augenklinik, Hamburg 20, Germany).

The membership fee has been set at 10 DM. (approximately U. S. $2.50) a year, payable in DM. or local currency.

Anyone residing in the Western Hemisphere and interested in this new Society is requested to contact Dr. Burian. All others should apply to Dr. Henkes.

ANNOUNCEMENTS

Oxford Ophthalmological Congress.—Mr. Ian C. Fraser, Secretary of the Oxford Ophthalmological Congress, has announced that the Congress will celebrate the 50th anniversary of its foundation at the annual meeting to be held July 1-4, 1959, at the University Laboratories of Physiology, South Parks Road, Oxford, England.

The main discussion will deal with "Ophthalmic Manifestations in Pediatric Practice." One day will be devoted to "After-Thoughts" on the Doyne Lecture delivered by each of the 15 past lecturers.

Postgraduate Course at Institute Barraquer.—A course for postgraduates in ophthalmology is being offered by the Institute Barraquer, Laforja, 88, Barcelona, Spain, during the period from November, 1959, to July, 1960.

Clinical sessions will be held from 8:00 to 4:00 o'clock on Mondays, Wednesdays, and Fridays. Students will be required to take part in functional explorations, including refraction, campimetry, ocular motility, and binocular vision, and to engage in objective explorations, such as biomicroscopy, gonioscopy, ophthalmoscopy, and tonography. Orthoptic and pleoptic sessions will be held.

On alternate days surgical sessions will convene.

The ophthalmic seminar will comprise three evening lectures each week. A systematic revision of ophthalmology will be considered. In addition, there will be lectures with discussions and presentations of clinical cases of the subject under consideration.

The purpose of this course is to insure a better training program for the accepted candidates. The number of candidates will be limited. Applicants will be selected on the grounds of merit subject to the approval of the Rectorial Board of the Institute.

The applicants should have the following minimum qualifications: title of a licentiate in medicine and surgery or the equivalent foreign degree. Applicants who have had one year's practice in the specialty at a clinic or an institute of

recognized scientific standing will receive preference.

Prof. Dr. Ignacio Barraquer will be Rector of the course. The faculty will include Dr. Joaquin Barraquer, Dr. Pascual Gonzalez-Marin, Dr. Alfredo Muinos Simon, Dr. Joaquin Rutllan, and Dr. Jose Maria Simon Tor.

Pan-Pacific Surgical Association Congress.—The Eighth Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, Sept. 28-Oct. 5, 1960.

All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons promises to be of interest to all doctors. Nine surgical specialty sections are held simultaneously.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Suite 230, Alexander Young Building, Honolulu 13.

Annual Meeting of the Pacific Coast Oto-Ophthalmological Society.—The Annual Meeting of the Pacific Coast Oto-Ophthalmological Society will be held May 3-7, 1959, at the Hotel Riviera, Las Vegas, Nev.

Guest speakers will be as follows:

R. R. Newell, M.D., Professor of Radiology and Biophysics, Ret., Stanford University School of Medicine;

William P. Mikkelsen, M.D., Associate Clinical Professor of Surgery, University of Southern California;

James F. Crow, Ph.D., Professor and Chairman, Department of Medical Genetics, University of Wisconsin;

Stuart C. Cullen, M.D., Professor and Chairman, Department of Anesthesia, University of California Medical Center;

George E. Shambaugh Jr., M.D., Professor and Chairman, Department of Otolaryngology, Northwestern University Medical School;

Sidney Riegelman, Ph.D., University of California School of Pharmacy;

Lawrence R. Boies, M.D., Professor and Chairman, Department of Otolaryngology, University of Minnesota;

Dean M. Lierle, M.D., Professor and Chairman, Department of Otolaryngology and Maxillo-Facial Surgery, State University of Iowa;

A. Edward Maumenee, M.D., Professor and Chairman, Department of Ophthalmology, The Johns Hopkins University;

John W. Henderson, M.D., Mayo Clinic;

Digby Leigh, M.D., Chief of Anesthesiology, Children's Hospital, Los Angeles.

For further information write Homer E. Smith, M.D., Executive Secretary-Treasurer, 686 12th Ave., Salt Lake City 3.

Basic Course in Orthoptics.—The Basic Course in Orthoptics for Technicians, sponsored by The American Orthoptic Council, will be held in the Department of Ophthalmology, University Hospital, Ann Arbor, Mich., from June 22 through Aug. 15, 1959. As usual, there will be didactic lectures and practical demonstrations, given by an outstanding faculty.

Further information as well as application blanks may be obtained by writing to John W. Henderson, M.D., Ann Arbor, Mich.

ANNUAL MEETING OF AMERICAN MEDICAL ASSOCIATION

Atlantic City, N. J., June 8-12, 1959

SECTION ON OPHTHALMOLOGY

Wednesday, June 10, 1959

Clinical Aspects of Ocular Siderosis and Hemosiderosis

PAUL A. CIBIS, St. Louis

TSUYOSHI YAMASHITA, St. Louis

FRANCISCO RODRIGUEZ V, St. Louis

Discussion to be opened by LORENZ E. ZIMMERMAN, Washington, D. C.

Ocular Manifestations of the Chronic Renal Tubular Insufficiency Syndromes
HAROLD F. FALLS, Ann Arbor, Mich.
Discussion to be opened by ISAAC S. TASSMAN, Philadelphia

Clinical Study of Choroidal Nevi
EDWARD TAMLER, San Francisco
A. EDWARD MAUMENEE, Baltimore
Discussion to be opened by JOSEPH A. C. WADSWORTH, New York

Embryonal Rhabdomyosarcoma of the Orbit in Children and Young Adults
WILLIAM C. FRAYER, Philadelphia
HORATIO T. ENTERLINE, Philadelphia
Discussion to be opened by WILFRED E. FRY, Philadelphia

Mycotic Ulcerative Keratitis
SHALER ROBERTS, Durham, N. C.
CAESAR GONZALEZ, Durham, N. C.
ERNEST CHICK, Durham N. C.
BANKS ANDERSON, Durham, N. C.
Discussion to be opened by FRANK W. NEWELL, Chicago

Applanation Tonometry in the Diagnosis and Treatment of Glaucoma
ANDREW J. GAY, St. Louis
BERNARD BECKER, St. Louis
Discussion to be opened by PETER C. KRONFELD, Chicago

The Application of the Television Ophthalmoscope to Some Problems of Clinical Ophthalmology
A. M. POTTS, Cleveland
S. S. WEST, Cleveland
J. SHEARER, Cleveland
Discussion to be opened by ARTHUR LINKSZ, New York

The Effect of α-Chymotrypsin on the Rabbit Zonule and Lens Capsule
ROBERT H. BEDROSSIAN, Vancouver
Discussion to be opened by RICHARD C. TROUTMAN, New York

Thursday, June 11, 1959

Executive Session

Clinical Aspects of Uveal Hypersensitivity
ROBERT S. COLES, New York
FREDERICK H. THEODORE, New York

Long-Term Steroid Therapy of Chronic Uveitis
DAN M. GORDON, New York
Discussion to be opened by IRVING H. LEOPOLD, Philadelphia

Effect of Levo-Rotary Adrenalin 2% on the Glaucomatous Eye
LAWRENCE L. GARNER, Milwaukee
WILLIAM JOHNSTONE, Chicago
ELMER J. BALLINTINE, Cleveland
MICHAEL CARROLL, Chicago
Discussion to be opened by WILLIS S. KNIGHTON, New York

Results of Iridencleisis in Negro and White Races
JOHN R. CASSADY, South Bend, Ind.
Discussion to be opened by SAMUEL D. MCPHERSON JR., Durham, N. C.

Ocular Manifestations of Pituitary Tumor in Cushing's Syndrome
THOMAS P. KEARNS, Rochester, Minn.
ROBERT M. SALASSA, Rochester, Minn.
COLLIN S. MACCARTY, Rochester, Minn.
JAMES W. KERNOHAN, Rochester, Minn.
Discussion to be opened by FRANCIS HEED ADLER, Philadelphia

Conjunctivo Antro Rhinostomy
James E. Bennett, Cleveland
James R. Armstrong, Cleveland
Raymond E. Jones, Cleveland
Fillmore Schiller, Cleveland
Discussion to be opened by Edmund B. Spaeth, Philadelphia

Friday, June 12, 1959

Panel on Neuro-Ophthalmology

Chairman's Address
Frank B. Walsh, Baltimore

Address of Invited Foreign Guest
S. P. Meadows, London, England

Ocular Manifestations of Tumors of the Brain Stem
Paul C. Bucy, Guest of Honor, Chicago
James E. Keplinger, Chicago

Ophthalmological Involvement in the Primary Demyelinating Diseases
Donald J. Lyle, Cincinnati

Some Neuro-Ophthalmological Considerations in Cerebral Vascular Insufficiencies
William F. Hoyt, San Francisco

Bilateral Central Scotomas of Hysterical Origin
Harvey A. Lincoff, New York

See-Saw Nystagmus with Suprasellar Epidermoid Tumor
J. Lawton Smith, Boston
Vernon H. Mark, Boston

Supratentorial Mass Lesions Presenting with Brain Stem Signs
Edward W. D. Norton, Miami, Fla.

Mascular Visual Fields
Charles J. Campbell, New York
M. Catherine Rittler, New York

Convergence Nystagmus
David G. Cogan, Boston

Panel to be discussed by S. P. Meadows, Paul C. Bucy, and Frank B. Walsh

"Dutch-Treat" Cocktail Party

to meet
Dr. Frank B. Walsh,
Chairman of Section,
and
Dr. S. P. Meadows and
Dr. Paul C. Bucy,
Guests of Honor

June 11, 1959, 5:30 to 7 p. m.
Ambassador Hotel, Renaissance Room
All physicians attending Section Meeting and their wives are invited.

Conference in Vancouver.—The 1959 British Columbia Oto-Ophthalmological Conference will be held in Vancouver, B. C., on May 28 to 30, 1959. Guest speakers will be Dr. Alfred Huber, Assistant to Professor Amsler, Zurich, Switzerland, in Ophthalmology, and Dr. T. E. Walsh, of St. Louis, in Otolaryngology. All Otolaryngologists and Ophthalmologists in the Pacific Northwest Area are cordially invited to attend.

Books

Emergency War Surgery, NATO Handbook. Price, $2.25. Pp. 411, including Index, with 18 illustrations. United States Government Printing Office, Washington, D. C., 1958.

This monograph on emergency war surgery very admirably fulfills the goal implied in its title. The general principles of various phases of emergency care of war injuries are outlined and very concisely discussed from a present-day point of view. The principles of mass casualties, the management of burns, shock and resuscitation, control of bleeding, and the management of bone and chest injuries are nicely reviewed.

The short section on the emergency management of injuries of the eye covers important principles of first-aid care of ocular injuries. Inexperienced persons are cautioned against manipulations of an injured eye. When penetrating injuries are suspected, litter evacuation is recommended. General surgeons are advised against removal of an eye unless (1) the globe is completely disorganized or (2) its removal is necessary as part of the general management of an extensive wound of the face. One might question the advisability of the first indication because there is no danger of sympathetic ophthalmia for ten days to two weeks and there is little likelihood of shock or dangerous infection. Prompt repair of injuries to the lids and especially of the lid margins is emphasized. This phase of treatment was often neglected in World War II and led to many unnecessary prolonged hospitalizations for later reparative surgery. Antibiotics or sulfonamides, very wisely, are prescribed systemically for the management of perforating injuries. The value of cortisone is discussed. This short section on ocular injuries could be read with profit by most ophthalmologists.

Furthermore, in this troubled world, every physician would be well advised to be familiar with the entire contents of the book. The future is so uncertain that need might arise at any time to render emergency care to family, friends, or neighbors.

Seltene Augengeschwulste. By Konstantin Pascheff. Translated into German by Dr. Ruth Borner. Price, not given. Pp. 140, with 42 illustrations. Akademie-Verlag, Mohrenstrasse 39, Berlin W 8, 1957.

This book in German is in two parts: the first considers unusual clinical and histologic forms of tumors of the eye and its adnexa; the second part deals with statistical investigations on ocular cancer as seen in Bulgaria, with some new points of view regarding its etiology, prophylaxis, and treatment. All of the malignant tumors, such as epithelioma, carcinoma, sarcoma, and glioma are included under the term "cancer," and of these the unusual forms are given special consideration. The text is illustrated with numerous photographs of gross specimens and microphotographs. It will probably be of considerable interest to pathologists who read German.

The Reproduction of Colour. By R. W. G. Hunt. Price, $12.75. Pp. 204, followed by index, with 87 figures, 10 color plates. The Macmillan Company, 60 5th Ave., New York 11, 1958.

This beautifully illustrated book has to do with color photography and color television from the technical point of view. For those with a reasonable facility with optics and the physics of light the book will be useful as a reference.

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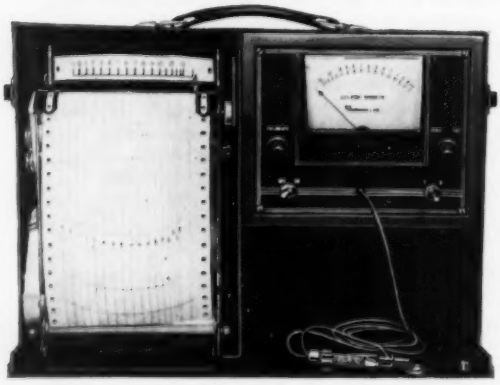

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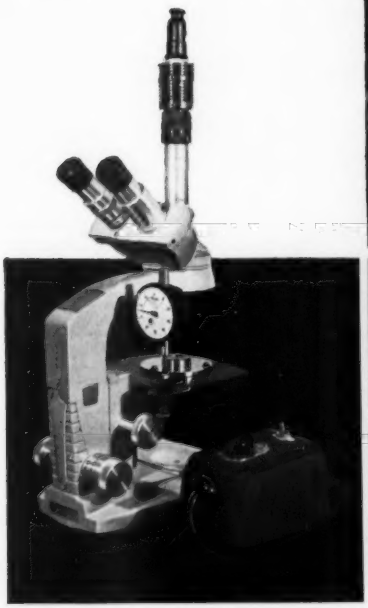

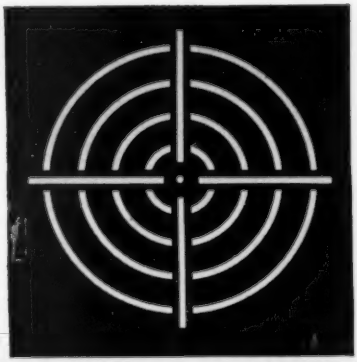

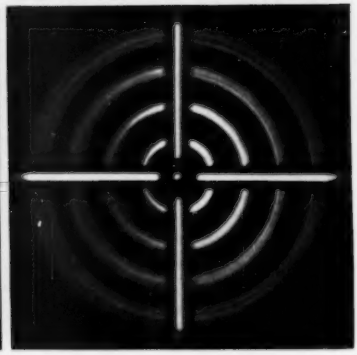

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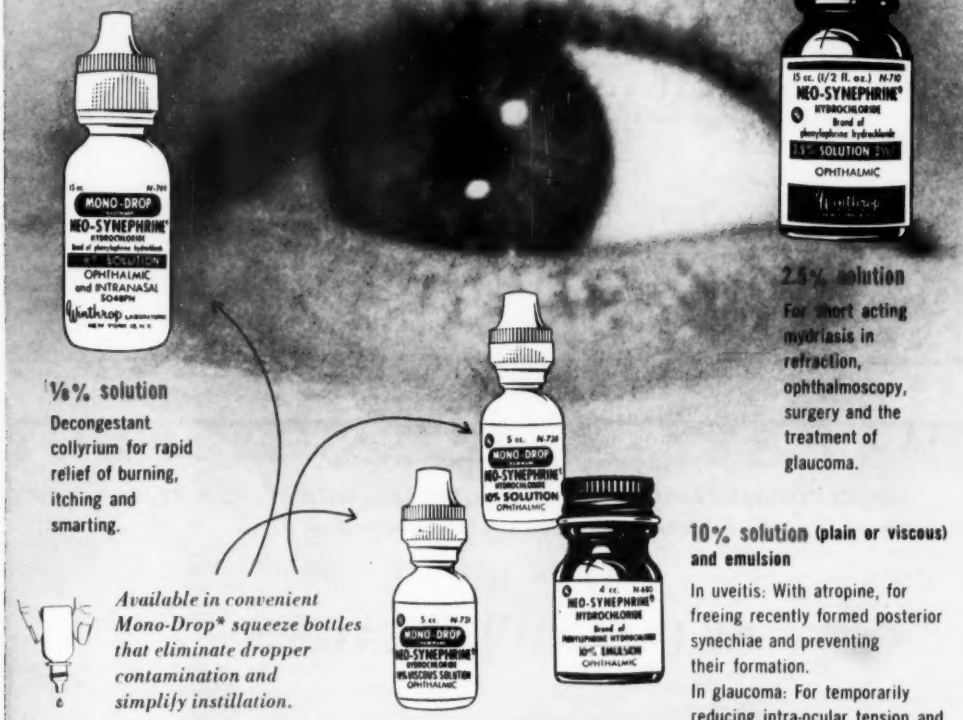

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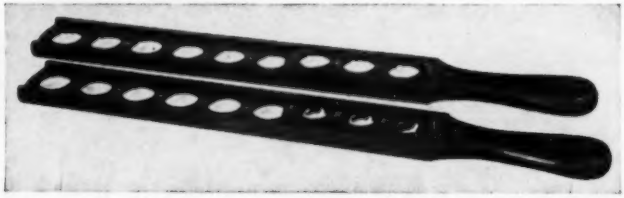

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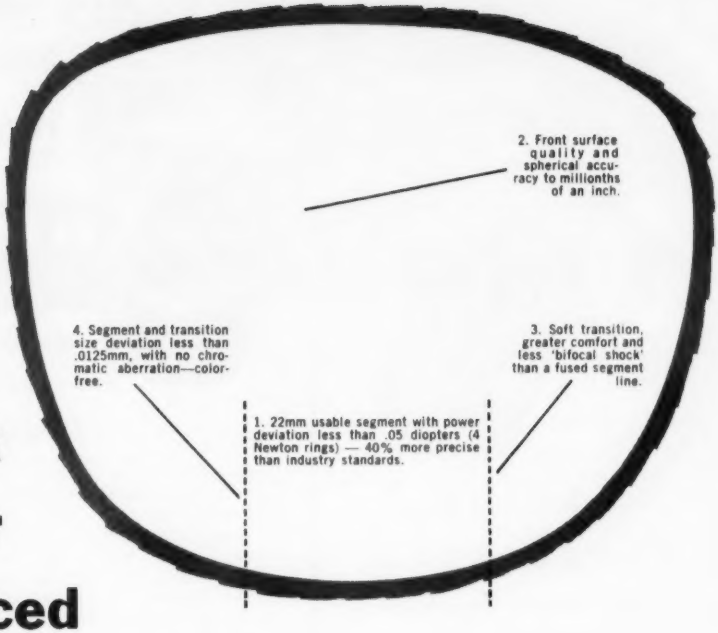
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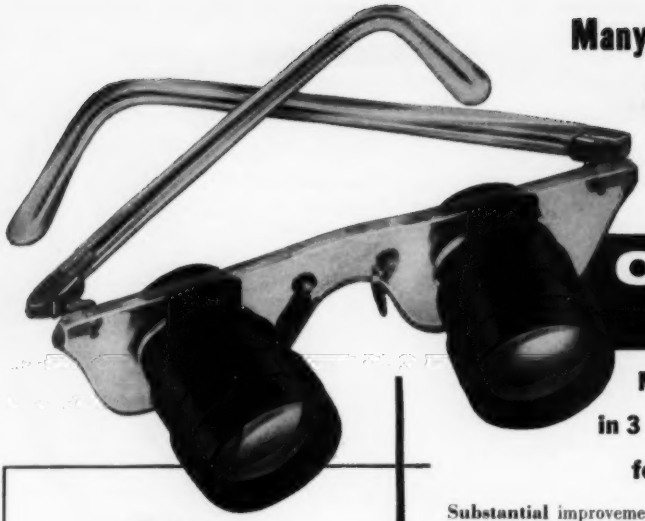

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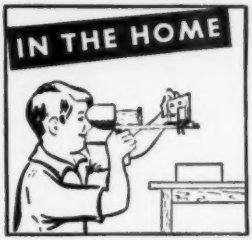

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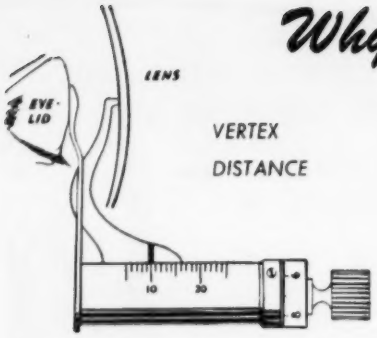

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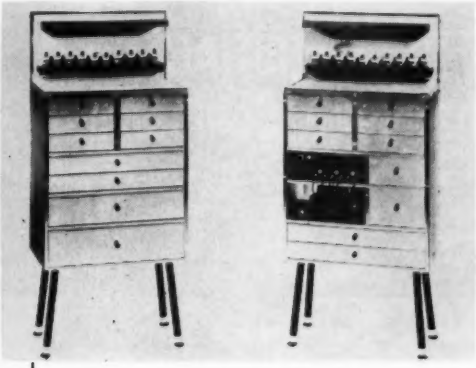

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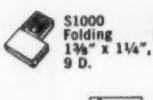

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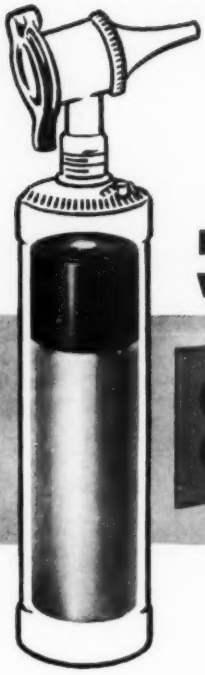

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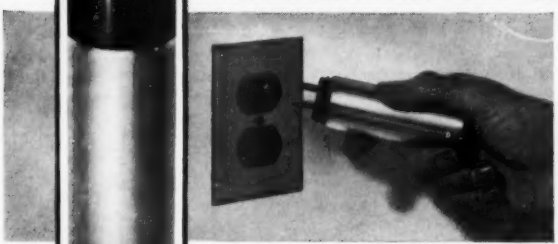

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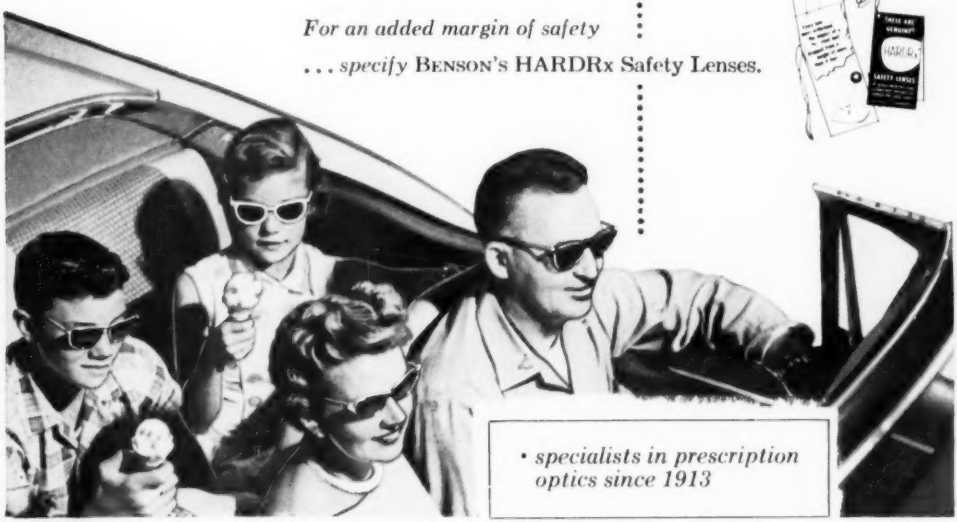

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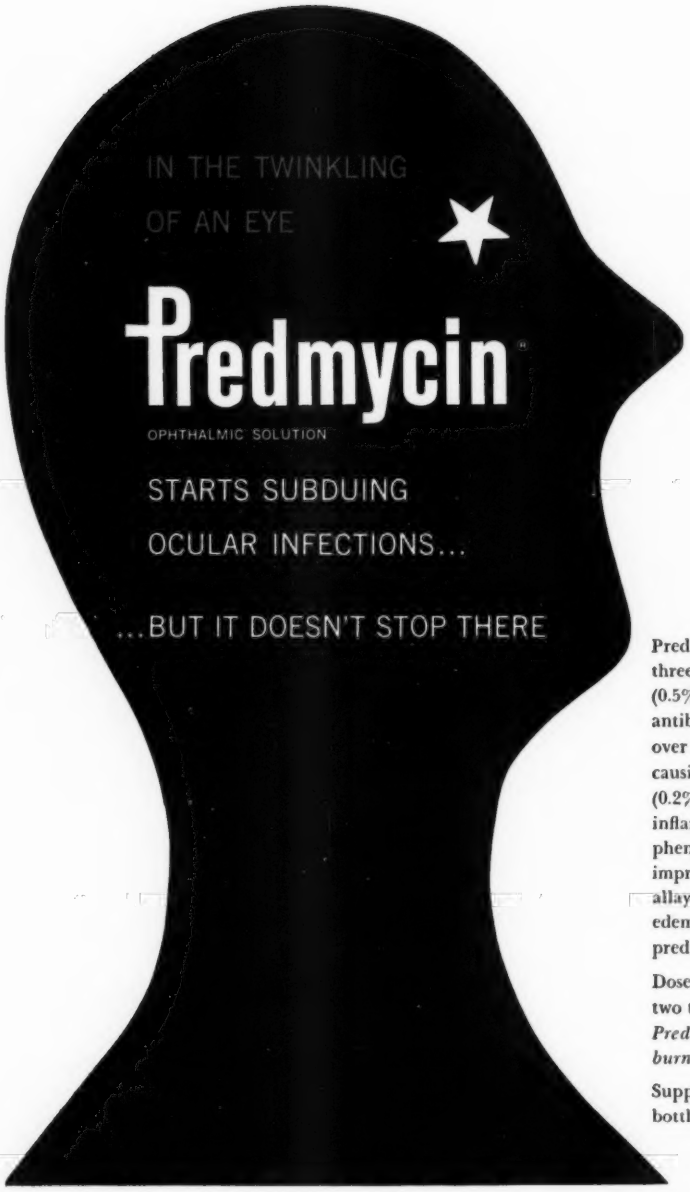

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